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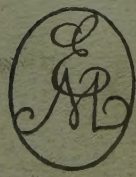
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VÄINÖ MÄKELÄ

VÄINÖ MÄKELÄ

1887—1943

Wenn der finnische psychiatrisch-neurologische Verein heute zu seiner Jahresversammlung und gleichzeitig zur ersten Versammlung während des Krieges zusammentritt, steht hier ein Platz leer. Eine uns allen bekannte Gestalt, ein Mann von stattlichem Wuchs, mit hoher Stirn, still und schlicht in seinem Gebaren, würdig, ohne diese Würde im mindesten zu unterstreichen, — Väinö Mäkelä ist nicht mehr da. Kameraden! Ihr wisst alle, was diese Tatsache für uns und für das von uns vertretene Gebiet hier im Lande bedeutet. Als Medizinalrat Väinö Mäkelä am 14. Juli 1941 aus dem Leben schied, wurde eine Arbeit unterbrochen, die die zielbewusste und einsichtsvolle Leitung der praktischen Psychiatrie und der Geisteskrankenpflege unseres Landes bedeutete. Es war dazu ein Werk, das für die kommenden Jahre noch reiche Früchte versprach. Auch wurde der Arbeit eines Gelehrten ein Ziel gesetzt, dem sein gründliches psychiatrisches Wissen, seine echt wissenschaftliche Denkweise und seine bereits vollbrachten Untersuchungen eine wichtige Stellung in der Wissenschaft seines Landes geschenkt hatten. Und wenigstens der, der ihn näher kannte, wusste auch, dass hinter allem diesem eine feste, unbestechliche Persönlichkeit stand.

Väinö Mäkelä wurde am 1. Januar 1887 in Lahti geboren. Seine Eltern waren der Landwirt Kalle Mäkelä und Wilhelmina Mäkelä. Das Abitur bestand er im Frühjahr 1905 an der Gemeinschaftsschule zu Lahti und begann danach mit seinen akademischen Studien in der physikalisch-mathematischen Sektion der

Gedächtnisrede, gehalten auf der Jahresversammlung des finnischen psychiatrisch-neurologischen Vereins (Suomen psykiatris-neurologinen yhdistys) am 5. 12. 1942.

philosophischen Fakultät der Universität Helsinki, um 1910 mit Chemie und Physik als Hauptfächern das philosophische Kandidatenexamen abzulegen. Damals ging er zur medizinischen Fakultät über und wurde 1913 Kandidat der Medizin. Auf diese Prüfung folgte der Dienst an den verschiedenen Kliniken in der hergebrachten Ordnung. In diesen Studienjahren war Mäkelä von seinen Kommilitonen ziemlich stark abgesondert, was sich teils aus seinem verschlossenen Charakter und teils daraus erklären dürfte, dass er sich als Kandidat der Philosophie erst später und in höherem Alter als seine Gruppenkameraden der betreffenden Studiengruppe anschloss. Wertschätzung und Achtung gewann er aber schon damals bei seinen Studiengenossen. Im Jahre 1919 legte Mäkelä die medizinische Lizentiatenprüfung, das medizinische Staatsexamen, ab. Schon vor dieser Prüfung hatte sich sein Interesse entscheidend der Psychiatrie zugewandt. Er war Amanuensis an der Zentralanstalt Lapinlahti gewesen, bekleidete dann 1918—20 verschiedene Vikariate an den Zentralanstalten Lapinlahti und Pitkämäki und wurde nach seinem Staatsexamen 1920 Assistenzarzt an der Anstalt Lapinlahti, als welcher er bis 1923 tätig war. Die Psychiatrie hatte ihn jetzt ganz in Beschlag genommen. Zum wesentlichen Teil wurde er für sie aber auch durch den Vertreter des Faches, Professor Christian Sibelius, gewonnen, dessen enthusiastisierende, warmerherzige Persönlichkeit Mäkelä ebenfalls eingenommen hatte. Zwischen dem Lehrer und dem Schüler entwickelte sich ein bis zu Sibelius' Tode bestehendes freundschaftliches Verhältnis, das allem Anschein nach auch später viel für Mäkelä bedeutet und sich bis in seine letzten Jahre positiv ausgewirkt hat.

Väinö Mäkeläs erste wissenschaftliche Arbeit war die 1916 in Finska Läkaresällskapets Handlingar erschienene Studie »Hernia diaphragmatica congenita spuria«, die im anatomischen Institut der Universität ausgeführt worden war. Mit seiner folgenden Arbeit, die 1917 in der Zeitschrift Duodecim erschien: »Imbesillin todistuskelpoisuudesta ja Sternin kuvametodin käytämisestä sen arvioimiseksi« (Über die Zeugnisfähigkeit des Imbezillen und die Anwendung der Sternschen Bildermethode zu ihrer Schätzung), betrat er auch schon in seinem literarischen

Schaffen entscheidend das Gebiet der Psychiatrie. Die Arbeit behandelte im Lichte eines einzelnen Falles die im Titel erwähnte Frage. Bei der Untersuchung gebrauchte Mäkelä neben dem uns aus den Intelligenzprüfungen bekannten Sternschen »Bauernstuben«-Bild ein einheimisches Bild, nämlich die farbige Wiedergabe des Gemäldes »Die Leichenwäscherinnen« von dem Künstler Rissanen, die sich recht gut zu dem Zweck zu eignen schien. Was die Bildermethode im allgemeinen betraf, zeigte der Fall nach der Ansicht des Verfassers ihre Verwendbarkeit bei dem Imbezillen, und Mäkelä wies darauf hin, wie man durch Benutzung zweier Bilder »einigermassen sehen kann, auf welche Weise verschiedene Vorstellungsbilder einander beeinflussen können«. Im Lichte seines Falles hebt Mäkelä zum Schluss hervor, »wie passive und gutartige Imbezille, deren angelerntes Wissen teilweise den Intelligenzdefekt verdeckt, vor Gericht auftreten können, ohne dass der Gerichtshof ihre Minderwertigkeit immer erkennt«. In den Akten waren die Äusserungen der untersuchten Person ganz tadellos, und gleichwohl zeigten die in dem Versuch gegebenen spontanen Aussagen, »wie überaus hilflos und wertlos ihre Beweise in der Tat sind«. Das Ergebnis seiner Arbeit fasst Mäkelä in dem Wunsch zusammen, dass »es angebracht wäre, der Anamnese der Zeugen und den Urteilen der Umgebung über sie mehr Beachtung zu schenken«.

In den Jahren 1919—21 breitete sich in Finnland, wie in grossem Umfang auch anderswo, die epidemische Enzephalitis aus mit verhängnisvollen Folgen für die körperliche und seelische Gesundheit vieler Individuen. Diese Krankheit war in jenen Jahren Gegenstand besonderer Aufmerksamkeit der medizinischen Welt, und der Untersuchung der durch sie verursachten seelischen Störungen ist die ausführliche, mühevollte Arbeit »Über psychische Störungen bei und nach der epidemischen Encephalitis« gewidmet, mit der Mäkelä im Herbst 1923 den Grad eines Doktors der Medizin und Chirurgie erwarb. Sie enthält die Ergebnisse von Untersuchungen, die der Verfasser an 21 Patienten mit der genannten Krankheit ausgeführt hatte, und ausserdem die Schlussfolgerungen, die sich auf klinischen Untersuchungen an einem noch umfangreicheren Patientenmate-

rial aufbauen. Durch genaue und vielseitige psychiatrische Prüfung versucht er in dem Werke festzustellen einerseits, was in den durch diese exogene Krankheit hervorgerufenen seelischen Störungen am wesentlichsten ist, und andererseits, welche Lokalisation im Gehirn diesen Veränderungen entspricht. Er kommt dabei zu dem Resultat, dass der wesentlichste Teil der bei dieser Krankheit auftretenden seelischen Störungen, ihr Skelett, nicht in solchen Symptomenkomplexen besteht, die im allgemeinen als für die exogenen Reaktionstypen kennzeichnend betrachtet werden, sondern vielmehr in den Störungen der allgemeinen seelischen Energie, des Gefühls- und Trieblebens und der Willenstätigkeit sowie insbesondere in der Störung der für den Denkverlauf und die seelische Tätigkeit überhaupt massgeblichen Leitung. Hinsichtlich der Lokalisation führen den Verfasser seine Erörterungen dahin, dass wahrscheinlich die wesentlichsten bei der Encephalitis epidemica vorkommenden Störungen von subkortikalen und vielleicht vor allem im Gehirnstamm gelegenen Krankheitsprozessen herrühren. Eine nähere Lokalisierung hält er jedoch nicht für möglich.

Im folgenden Jahr, 1924, veröffentlichte Mäkelä die Studie »Von Auffassungsstörungen in einem Falle von Eklampsie und von dem Verhalten der eklamptischen psychischen Störungen zu den sogenannten Reaktionstypen«. In dem hier beschriebenen Fall konstatierte er bei einer plötzlich an einem eklamptischen Zustand erkrankten Frau im 8. Schwangerschaftsmonat einen 2 Wochen dauernden psychischen Krankheitszustand, dessen charakteristischer Zug in einer eigenartigen Störung der Auffassung von Ganzheiten bestand. Diese Störung betraf sowohl die Fähigkeit, die optischen Empfindungen als Ganzes aufzufassen, wie z. B. die Fähigkeit, die Zeit aufzufassen. Auch die letztere spaltete sich in kleine, aufeinanderfolgende Fragmente auf. Auf dieser Störung beruht nach der Ansicht des Verfassers auch die in diesem Fall nachgewiesene Alexie. Im Schrifttum fand er mehrere Fälle, die, zumal wenn die Untersuchung exakt ausgeführt worden war, wesentlich an den von ihm untersuchten Fall erinnerten und zu der Annahme führten, dass die bei der Eklampsie auftretende Noxe eine gewisse Affinität zu den

optischen und den enger mit ihnen zusammenhängenden Gehirnapparaten besitzt. Und er äussert Worte, die für seinen nach genauer und gründlicher Forschung verlangenden Charakter recht kennzeichnend sein dürften: *»Überdies enthalten die Fälle die Aufforderung, jede eklamptische Psychose genauer zu untersuchen; vielleicht finden sich tatsächlich gemeinsame Züge und nicht nur farblose exogene Reaktionstypen.«* Und fast als eine Programmankündigung kann der Schluss des Aufsatzes gelten, den ich hier in extenso zitiere: *»Bei akuten und stürmisch verlaufenden Fällen von Psychose ist es recht schwer, das Krankheitsbild zu analysieren sowie unmöglich, auch nur die verschiedenen Typen voneinander zu unterscheiden. Daher müssen wir von leichteren und kaum zu den Psychosen zu rechnenden Fällen ausgehen und versuchen, zunächst durch deren genaue Untersuchung eine gemeinsame Grundlage für den weiteren Fortschritt zu schaffen.*

Natürlich führt uns auch die psychologische Analyse allein nicht weit, sondern wir müssen auch die anderen verfügbaren Untersuchungsmethoden zu Hilfe nehmen. Wir müssen überdies in jedem symptomatischen Psychosefall zu klären versuchen, welche Rolle bei der Entstehung der Psychose und des Psychosebildes eventuell folgende Umstände spielen: die Konstitution des ganzen Körpers, und zwar besonders des Gehirns und der Gehirnpartien, konditionelle allgemeine und spezifische Momente, die Noxe und deren Veränderungen, während der Wirkungsdauer der Noxe eventuell hinzutretende Umstände, sowie die mit den vorstehenden Punkten im Abhängigkeitsverhältnis stehende Lokalisation des Krankheitsprozesses. Hier können jedoch Einzelfälle keine Beweiskraft haben; ebensowenig wie ein psychologisch analysierter Fall die ganze Psychose erklärt, ebensowenig liefert eine in der Familie eines Falles gefundene sog. endogene Psychose oder die in einer bestimmten Richtung verlaufende Persönlichkeit eines Kranken ein Zeugnis für die spezifisch bestimmende Stellung der Konstitution auch nur in diesem einen Falle. Nur mühevollles Sammeln führt uns möglicherweise zum Ziele, von dem wir noch weit entfernt sind.«

Hier spricht ein wirklicher Gelehrter und ein seiner Verant-

wortung als Wahrheitssucher bewusster Forscher. Ich möchte ausserdem sagen, hier spricht speziell ein nordischer Forscher.

Väinö Mäkelä hatte jetzt die besten Voraussetzungen, seine wissenschaftliche Arbeit fortzusetzen. Während seiner Assistenzarztjahre in Lapinlahti hatte er sich mit der klinischen Psychiatrie und während seiner wissenschaftlichen Arbeit und durch seine Studien mit der psychiatrischen Literatur bekannt gemacht. Aber er hatte sich vor allem tief in dieses Gebiet eingelebt, und als er einige Jahre später einmal im vertraulichen Gespräch halb im Scherz bemerkte, dass er die Psychiatrie kenne, sprach er die Wahrheit. Nach Abschluss seiner Assistenzarztperiode und seiner Dissertation begab er sich denn auch, mit einem Stipendium der Kordelin-Stiftung ausgerüstet, nach München, um dort an der Deutschen Forschungsanstalt für Psychiatrie und daneben auch am Hirnverletzten-Institut zu arbeiten. Aber die Reihe seiner wissenschaftlichen Veröffentlichungen erfuhr doch eine lange Unterbrechung. Seiner Natur lag alle Pfuscherei fern. Ausserdem scheint es sich hier im Norden so zu verhalten, dass wir arm an Männern und diese Männer arm an weltlichen Gütern sind. Daher können wir einen fähigen Mann nicht allein seiner wissenschaftlichen Arbeit überlassen, und auch er selbst kann sich ihr nicht ganz widmen, sondern er wird wenigstens auf seinem Fachgebiet für praktische Aufgaben in Anspruch genommen. So ging es auch mit Mäkelä, als er 1925 zum Chefarzt und Leiter der Zentralanstalt Pitkämäki ernannt wurde. Der Wissenschaft wollte er freilich nicht entsagen, und am allerwenigsten verzichtete er damals auf die wissenschaftliche Basis, die auch das A und O seiner praktischen Tätigkeit war. Aber notgedrungen beschränkte sich die Zeit, die er rein wissenschaftlicher Arbeit widmen konnte, auf das Geringste. Dagegen hatte die Irrenpflege des Landes einen Arbeiter bekommen, der ihr mit seinem Wissen, seiner Geschicklichkeit und seiner Energie unersetzliche Dienste leisten sollte.

Mäkelä war in der Irrenpflege vor allem von einem Streben beseelt: Die Kranken sollten behandelt und nicht bloss am Leben erhalten werden. Er bekämpfte von Anfang an und unnachgiebig die Auffassung, die er die »Magazinauffassung« nannte, die

das Krankenhaus zu einem Magazin machte und den Arzt zu dessen Wächter erniedrigte. Daher fand alle »aktive« Pflege in ihm einen warmen Anhänger und Anwender. Er nahm an seinem Krankenhaus eine effektive Arbeitstherapie in Gebrauch und begann sie systematisch zu entwickeln, daneben aber interessierte ihn in hohem Grade auch die übrige Psychotherapie, und diese gehörte für ihn als Anstaltsarzt zu den Verfahren, die er mit gutem Erfolg anwandte. Auch die Malariakur wurde unverzüglich dem Behandlungsprogramm des Krankenhauses einverleibt. Mäkelä wollte auch die Neurosen in den Bereich der psychiatrischen Tätigkeit einbeziehen und zugleich seinerseits die Vorurteile brechen, die die Irrenpflege von der übrigen Behandlung der Nervenkrankheiten zu trennen wünschten. Aus diesem Streben ergab sich die Einrichtung einer besonderen Abteilung für Nervenkrankheiten oder Grenzzustände am Krankenhaus Pitkänniemi 1927. Immer grösseren Anteil nahm Mäkelä auch an der Kinderpsychiatrie, was u. a. die Untersuchungen zeigen, die er im Auftrag des Oberinspektors für Kinderschutz, Baron Adolf von Bonsdorffs, in den Erziehungsanstalten Koivula und Vuorela ausgeführt hat. Gleichzeitig mit der Abteilung für Nervenkrankheiten wurde in Pitkänniemi auch eine psychiatrische Kinderabteilung gegründet, der Mäkelä ein besonders warmes Interesse schenkte. Über die sonstige Leitung eines Krankenhauses war er der Ansicht, der Chefarzt müsse ein Programm für den Zweck, dem die Anstalt dienen solle, schaffen, und danach müsse sich sowohl das Personal wie alles andere so in dieses Programm einfügen, dass das Krankenhaus zu einem abgerundeten Ganzen und einem jenem bestimmten Zweck dienenden Werkzeug werde.

Nur vier Jahre konnte Mäkelä als Chefarzt von Pitkänniemi wirken. Er trat 1929 von diesem Amt zurück und reiste von neuem nach München, um seine wissenschaftliche Arbeit an der Deutschen Forschungsanstalt für Psychiatrie fortzusetzen. Seine Untersuchungen, die er beinahe drei Jahre in München weiterführte, betrafen die Genealogie der traumatischen Epilepsie. Die Arbeit wurde mit der Mäkelä eigenen Gründlichkeit und Vertiefung in den Gegenstand geleistet und umfasste ein grosses

und wertvolles Material von Gehirnbeschädigten. Sie interessierte im höchsten Grade die wissenschaftliche Anstalt, in deren Bereich sie ausgeführt worden war, und die davon einen ausserordentlich wertvollen Beitrag zu der Reihe ihrer Untersuchungen erwartete. Nach seiner Heimkehr beschäftigte sich Mäkelä weiter mit der Arbeit, aber leider konnte er sie vor seinem Tode nicht mehr vollenden.

Nachdem Mäkelä 1932 nach Finnland zurückgekehrt war, widmete er sich anfangs seiner wissenschaftlichen Arbeit und psychiatrischer Privatpraxis in der Hauptstadt. Wie früher verwandte er auch jetzt viel Sorgfalt und Zeit auf seine Patienten. Ähnlich wie in seine Forschung vertiefte er sich in den einzelnen von ihm behandelten Krankheitsfall gründlich und gewissenhaft. Er war ein lebhaft interessierter Psychotherapeut und als solcher auch erfolgreich, wozu sowohl seine Vertiefung in die Schwierigkeiten und Konflikte des Patienten als auch der starke Einfluss seiner eigenen Persönlichkeit auf den Kranken beigetragen haben dürfte. Er bewahrte diesen Glauben an die Bedeutung der Psychotherapie neben seinem Interesse für die psychiatrische Genealogie und auch trotz der neuzeitlichen somatischen Ausrichtung der psychiatrischen Therapie, die er ebenso wie ihre Leistungen zugleich voll und ganz einzuschätzen wusste.

Auf dem 1935 in Stockholm abgehaltenen Nordischen Psychiatrischen Kongress, als dessen einer Vizepräsident Mäkelä tätig war, und dessen Hauptthema die allseitige Erörterung des Schizophrenieproblems war, erstattete er ein Referat über die Psychopathologie des Spaltungsirreseins, wobei er recht selbstständige Gedanken darlegte. Seiner Ansicht nach waren »die Persönlichkeitsstörungen im Ich selbst und seiner Beziehung zur Aussenwelt« zentrale Symptome im psychischen Krankheitsbild. Er zeigte, wie im Wahrnehmen, im Denken, im Gefühls- und Willensleben dieselbe Spaltung der Komplexe stattfindet, und wie dadurch »all die Energie, über die der Schizophrene verfügt, vor grosse und oft unüberwindliche Schwierigkeiten gestellt wird. So kann man es erklären, dass die Energie oft unzureichend oder falsch ausgerichtet ist und ein vielschichtiges Schizophreniebild mit Minus- und Plusmomenten entsteht.«

Einige Jahre später wurde Mäkelä aus seiner privaten ärztlichen Tätigkeit und von seinem wissenschaftlichen Material weg zu wichtigen sozialen Aufgaben geführt. Es begann die letzte von Arbeit erfüllte Periode seines Lebens, deren Inhalt vor allem die Entwicklung der Irrenpflege und der sozialen Psychiatrie in unserem Lande bildete. Am 16. Juli 1935 wurde er in das wissenschaftliche Kollegium der Medizinalverwaltung als die Erblchkeitslehre vertretendes Mitglied berufen. Als Sachverständiger hatte er schon früher an der Ausarbeitung des Sterilisationsgesetzes und der daran anschliessenden Verordnung teilgenommen und trug jetzt nach ihrem Inkrafttreten als Persönlichkeit, deren Ansicht von sehr entscheidender Bedeutung war, wirksam zu ihrer Anwendung bei. So hat er in dieser wichtigen Frage Traditionen geschaffen und den Weg abgesteckt. Sein 1936 in der Zeitschrift des Ärzteverbands Finnlands erschienener 100 Seiten starker Aufsatz »Suomen ja muiden Pohjoismaiden sekä Saksan sterilisoimis- ja kastroimislain säädäntö« (Die Sterilisations- und Kastrationsgesetzgebung Finnlands und der anderen nordischen Länder sowie Deutschlands) erweist, wie gründlich er sich auch mit dieser Frage vertraut gemacht und in sie eingelebt hatte. Später, 1937, stellt er im »Archiv für Rassenbiologie« dem ausländischen Leserkreis unter dem Titel »Die Sterilisations- und Kastrationsgesetzgebung in Finnland« die neue Gesetzgebung auf diesem Gebiet dar, und 1939 behandelt er in der Festschrift für Antti Tulenheimo in einem Aufsatz »Epilepsia Suomen avioliitto- ja sterilisoimislain säädännössä« (Die Epilepsie im Eherecht und in der Sterilisationsgesetzgebung Finnlands) die Frage der Erblchkeit der Epilepsie, die Differentialdiagnose zwischen der genuinen und der exogenen Fallsucht und die Beziehung des Sterilisationsgesetzes zu diesen Fragen. Dabei dienen ihm als Grundlage teilweise eigene Untersuchungen über die Heredität an traumatischer Epilepsie Leidender. An die Sterilisationsfragen schliesst sich endlich 1938 ein Aufsatz »Holhoojan (uskotunmiehen) toiminta sterilisoimislain puitteissa« (Die Tätigkeit des Vormunds (Treuhänders) im Rahmen des Sterilisationsgesetzes) in der Zeitschrift Lakimies 1938 an, worin er die Gründe motiviert,

aus denen die Medizinalverwaltung zu der Forderung gelangt war, dass in dem von § 1 Absatz 1 des Gesetzes vorausgesetzten Sterilisationsfall im allgemeinen immer ein Gutachten des Vormunds oder Treuhänders beschafft und nötigenfalls eine solche Person speziell für diesen Zweck bestimmt werden sollte. Medizinalrat Mäkelä begründet diesen Standpunkt in seinem Aufsatz u. a. damit, dass »die Erfahrung gelehrt hat, dass man leicht in Schwierigkeiten gerät, wenn das Gesetz in dieser Beziehung zu weit und unbestimmt ausgelegt wird. Ausserdem könnte dabei im Gemeinwesen leicht ein Gefühl der Unsicherheit und Schutzlosigkeit und sogar Widerstand entstehen, der dazu angetan wäre, die Anwendung des erforderlichen Sterilisationsgesetzes zu gefährden. Namentlich empfindliche, psychopathische Menschen würden leicht das Gefühl des Rechtsschutzes verlieren, wenn geistig Minderwertige und Wehrlose wenigstens anscheinend rücksichtslos sterilisiert würden. Und das Gesetz würde auch unnötigerweise in solchen Fällen als Zwangsgesetz gedeutet werden, wo dies nicht am Platze wäre.«

Im Jahre 1936 bewarb sich Mäkelä um das Amt des Medizinalrates der Abteilung für Irrenpflege bei der Medizinalverwaltung, wurde zu demselben ernannt und begann es am 1. Januar 1937 zu verwalten. Diese Entscheidung war ein bedeutender Gewinn für die Irrenpflege im Lande und für deren Weiterentwicklung. Es war in Finnland kein anderer Mann zu finden, der, tief mit der Psychiatrie vertraut, zugleich das Gebiet, die Krankenhausorganisation und das Krankenhauswesen überhaupt, die Verwaltungsfragen, die Ausbildung des Personals, die soziale Psychiatrie, die einschlägige Gesetzgebung usw. gleich vollständig beherrscht hätte. Es begann denn auch sofort eine energische Arbeit, die sich während der 4½ Jahre ihrer Dauer immer vielseitiger und tiefgreifender gestaltete. Im ersten Jahre der Tätigkeit nahm der Reichstag das in seinem vorbereiteten Stadium viel umstrittene neue Geisteskrankengesetz an, und die daran anschliessende Verordnung wurde am 22. Dezember desselben Jahres veröffentlicht. Gewisse mit ihrer Ausführung zusammenhängende Aufgaben wurden dem neuen Medizinalrat übertragen. Sowohl das Gesetz als die Verordnung traten An-

fang 1938 in Kraft. Aber die auf ihrer Basis stattfindende Tätigkeit musste mit Geist erfüllt werden. Mäkelä folgte bei der ihm vorliegenden umfassenden Arbeit seinen früheren Leitsterren. Der Boden musste von zweierlei Art sein — ein psychiatrischer und ein sozialer. Die Voraussetzung dafür, dass sich die Pflege der Geisteskranken auf ein hohes Niveau erhob, bestand darin, dass das Niveau der die Arbeit Leitenden — der Ärzte — hoch genug war. Daher musste ihre Ausbildung intensiviert, den künftigen Ärzten die Bedeutung und die Möglichkeiten der Psychiatrie klargemacht, die Ausbildung der Fachärzte psychiatrisch möglichst sachgemäss durchgeführt werden, während sie gleichzeitig zu sozialer Wirksamkeit angehalten und schliesslich ihr Interesse an der Arbeit fortgesetzt genährt wurde. Das war um so wichtiger, als besonders die an den Kreisirrenanstalten arbeitenden Ärzte bei Geltendmachung therapeutischer Gesichtspunkte oft gegen Vorurteile und u. a. gegen engherzig wirtschaftliche Auffassungen ankämpfen mussten. Von Anfang an bemühte sich daher Mäkelä um eine engere Fühlung mit diesen Kollegen. Seit 1937 wurden auf seine Initiative die leitenden Ärzte der Kreisirrenanstalten zu zweimal im Jahre stattfindenden gemeinsamen Beratungen in die Medizinalverwaltung eingeladen. Der Gedanke wurde, wie Mäkelä in seinem Bericht über die Tätigkeit der Irrenpflegeabteilung der Medizinalverwaltung in den Jahren 1928—1937 mitteilt (Die Irrenpflegeabteilung der Medizinalverwaltung in den Jahren 1928—1937), günstig aufgenommen. Die leitenden Ärzte stellten sich zahlreich zu den Zusammenkünften ein und berichteten selbst über aktuelle Fragen der Irrenpflege, über die anschliessend diskutiert wurde. So wurden in den Versammlungen des ersten Jahres so wichtige Dinge besprochen wie die Mittel und Wege zu einer hinreichenden Intensivierung der Irrenanstalten, die Ausbildung der Pfleger und Pflegerinnen, die ökonomische Stellung der Praktikanten, die Grösse des Personals und die Staatsunterstützung der Kreisirrenanstalten. Die Versammlungen waren offenbar ausserordentlich nützlich sowohl für die eingeladenen Teilnehmer und die durch sie auszuführende »Feldarbeit« als auch für die die Irrenpflege leitenden Persönlichkeiten, die auf diese

Weise mit ihnen in Kontakt kamen. Das geschah auch durch freien Verkehr im Anschluss an die Zusammenkünfte, für den das gemütliche und gastfreundliche Heim Mäkeläs, in dem alle diese Bestrebungen sich widerspiegeln, den äusseren Rahmen und das günstigste Milieu gab. Bemerkenswert ist auch, wie Väinö Mäkelä, dieser ursprünglich so verschlossene und sich nur wenigen öffnende Mann, sich immer mehr zu einer sammelnden Persönlichkeit entwickelte, die andere um sich zu scharen und ihnen auch immer etwas zu geben vermochte.

Wie auch aus dem Obigen hervorgeht, war es Mäkeläs Wunsch, die Kreisirrenanstalten und die Tätigkeit ihrer Ärzte in jeder Hinsicht zu unterstützen. Es gab aber eine andere Art von »Krankenhäusern«, denen zu Leibe zu gehen er sich für verpflichtet hielt. Das waren die Irrenabteilungen der Kommunalheime. Die Frage ihrer Existenz und Verwendung war für ihn schon lange massgeblich und wichtig gewesen. In dem oben erwähnten Zehnjahresbericht sagt er: »Sie sind keine Heilanstalten für Geisteskranke und können nie zu solchen werden. Daraus folgt aber auch unbedingt, dass sie zu einem unerlaubten Zweck gebraucht werden, wenn darin akute Patienten länger als zulässig und chronische Geisteskranke in Zellen isoliert gehalten werden. Diese Missstände müssen möglichst bald schon als gesetzwidrig beseitigt werden.« Nachdem er noch die mit diesen Abteilungen verknüpften Übelstände geschildert hat, die auch durch Ausbesserungen nicht geändert werden können, kommt Mäkelä zu dem Schluss, dass die Abteilungen bei ganz anderer Verwendung von grosser und wesentlich anderer Bedeutung und wirklich von Nutzen sein könnten, wobei auch die für sie geopfertten Mittel nicht vergeudet würden. So kehrt er zu seinem Lieblingsgedanken und seinem bereits über zehn Jahre alten Plan zur Regelung der psychiatrisch-sozialen Fürsorge auf dem platten Lande zurück. Die Irrenabteilungen der Kommunalheime wären »in helle Wohngebäude zu verwandeln, in denen chronische, arbeitende Geisteskranke untergebracht werden«. Die Abteilungen sollen der Aufsicht eines Psychiaters unterstellt werden, am besten vielleicht so, dass die Kreisirrenanstalten als Zentralen dienen und einer ihrer Ärzte als oberster Aufseher über die Irrenabteilungen der Kommunalheime der Umgebung fungiert.

Um diesen Plan durchzuführen, wären die Bezirke der Kreisirrenanstalten zu revidieren und neu zu ordnen. Da man aber durch diese Mittel noch nicht alle Geisteskranken, die auch seitens der Armenpflege in Familien untergebracht sind oder bei ihren Angehörigen oder in gewöhnlichen Irrenabteilungen wohnen, in psychiatrische Kontrolle und Fürsorge bekäme, wären in der Nähe der Irrenanstalten kleine, einfache Wohnkolonien zu erstellen und in den Kommunalheimen die erforderlichen Räume für gelegentliche Pflege einzurichten.

Die Kinderpsychiatrie zog Mäkelä dauernd an, und die Durchführung praktischer Massnahmen auf diesem Gebiet war für ihn eine Herzenssache. Im Auftrag des psychiatrisch-sozialen Ausschusses bei dem Kinderschutzverband General Mannheims hatte er früher einen Vorschlag über die Einrichtung einer Beobachtungs- und Fürsorgezentrale für nervöse und psychisch anormale Kinder ausgearbeitet. In der letzten Jahren waren auch noch andere auf diese Fragen sowie auf die Pflege epileptischer Kinder bezügliche Anregungen gegeben worden. Jetzt brachte Mäkelä diese Angelegenheit von neuem aufs Tapet, und auf seine Anregung beantragte die Medizinalverwaltung 1937 beim Staate die Organisation einer Kinder-Beobachtungs- und Fürsorgeanstalt, die über alle erforderlichen Vorrichtungen verfügen und aus drei Teilen bestehen sollte: einer Poliklinik, mehreren Versuchsschulklassen und einem Krankenhaus. Das letztere sollte drei Abteilungen umfassen: eine Abteilung für Kinder mit schweren Psychosen, eine Abteilung für Epileptiker sowie eine Abteilung für Patienten mit ganz leichten psychischen Störungen und Nervenkrankheiten. Alle diese Abteilungen sollten von Personen betreut werden, die mit der Kinderpsychiatrie, der Neurologie, den Kinderkrankheiten, der Psychologie und der Pädagogik bekannt waren.

1937 war im Reichstag beantragt worden, die Anordnung besonderer Pflege und Erziehung von schwierigen Kindern und Kindern mit antisozialen Neigungen zu untersuchen. 1939 wurde Mäkelä zum Vorsitzenden eines Staatskomitees verordnet, das Vorschläge über die Organisation der Behandlung solcher Kinder ausarbeiten sollte.

Zu den Plänen des Medizinalrates Mäkelä gehörte ferner die

Gründung eines grossen für den Staat und die Gemeinden gemeinsamen modernen Nerven- und Irrenkrankenhauses in der Provinz Uusimaa, das therapeutischen und Ausbildungszwecken, möglicherweise auch als Universitätsklinik der psychiatrischen Schulung der Ärzte dienen sollte. Fragen betreffend die Pflege der Kriminalpatienten und strafrechtliche Gutachten über den Geisteszustand, die Regelung der Therapie der Nervenkrankheiten und Neurosen und manche anderen Fragen und Pläne füllten seinen langen Arbeitstag aus. Seine Bestrebungen konzentrierten sich, kann man sagen, darauf, was er selbst in dem schon oben erwähnten Zehnjahresbericht im Zusammenhang mit dem angedeuteten Fürsorgeprogramm sagt: »Von Wichtigkeit wäre es jedoch, dass jeder einzelne psychisch Kranke untersucht und sachgemäss behandelt würde. Und das lässt sich durch Gebäude und Krankenplätze allein nicht erreichen. Die Pflege in den heutigen Krankenhäusern muss wirksamer gestaltet werden, so dass die Zahl der Aufnahmen erhöht werden kann, und dass sie nicht für einen Augenblick von ihrer Aufgabe und ihrem Ziel abweichen: es muss versucht werden, die Patienten gesund zu machen.«

Im Jahre 1933 wurde Mäkelä zum Vorstandsmitglied der Gesellschaft für psychische Gesundheit und 1937 zum Vorsitzenden der Gesellschaft gewählt. Auch in dieser Eigenschaft konnte er viel Arbeit ausführen und zahlreiche Initiativen ergreifen. Von diesen seien hier nur die der letzten Zeit erwähnt: die Organisation der Pflege der zu den Umsiedlern gehörenden Kranken und der Gehirnverletzten. Auf seine Anregung erhielt die Gesellschaft den Namen »Verein zur Bekämpfung der Nerven- und Geisteskrankheiten«.

In diesem unserem Verein, dem psychiatrisch-neurologischen Verein Finnlands, nahm Mäkelä eine zentrale Stellung ein. Viele Male haben wir hier seine Vorträge über wissenschaftliche Fragen gehört, und zahlreich sind auch die Berichte und Äusserungen über die Irrenpflege, die er hier gegeben hat. Von den letzten sei vor allem das grosse Programm zur Organisation der Irrenpflege, der psychiatrischen Fürsorge, der ärztlichen Ausbildung usw. genannt, das er dem Verein in der Frühjahrssitzung 1941

vorlegte. Auf nordischen Kongressen hat er den Verein und die psychiatrische Wissenschaft unseres Landes auf hervorragende Weise vertreten. 1935 war er in Stockholm und 1938 in Oslo als einer der Vizepräsidenten tätig, und auf beiden Tagungen hielt er auch Referate, auf der ersten, wie bereits erwähnt, über die Psychopathologie der Schizophrenie, auf der anderen über die Einteilung der Neurosen. Das Referat ist in den *Acta-psychiatrica et neurologica* veröffentlicht unter dem Titel: »Über die Abgrenzung der Neurosen und ihre Einteilung in Untergruppen mit besonderer Berücksichtigung der Formen, die den endogenen Psychosen nahestehen.« Als allgemeine Grundlage der Neurosen betrachtete er die psycho-somatische Eigenart des Individuums, die auf irgendeine Weise als erblich betrachtet werden muss und die unter verschiedener Gestalt und mit verschiedener Stärke auftritt. Diese Eigenart äussert sich in mangelhafter und unwirtschaftlicher Fähigkeit, durch äussere Reize entstandene Erlebnisse zu beherrschen. Auf dieser Basis entwickeln sich dann die neurotischen Reaktionsmöglichkeiten. In dem Aufsatz spricht der Verfasser dann vor allem von der Neurasthenie, der Psychogenie, der Hysterie und dem anankastischen Symptomenkomplex und hält sich namentlich bei der Differentialdiagnose zwischen diesen Zuständen und den endogenen Psychosen auf.

Ich habe hier die reichen Voraussetzungen zu skizzieren versucht, die Väinö Mäkelä schon durch seine Begabung auf den Lebensweg mitbekommen hatte, die Leitsterne, denen er in seiner ganzen Tätigkeit als Arzt und Psychiater getreu folgte, und die vielseitige Arbeit, die er auf seinem Wirkungsfeld ausführen konnte. Ich habe bei meiner Schilderung auch in verschiedenem Zusammenhang auf die Entwicklung hinzuweisen versucht, die in ihm vor sich ging. Er war wohl mit seinem athletischen Bau, seinem prächtigen Kopf und seiner Gemütsart der Grundtyp einer hochstehenden schizothymen Persönlichkeit. Er war ein verschlossener Charakter. Aber diese Verschlossenheit wies von vornherein Lücken auf. Dem Kameraden, in dessen Gesellschaft er sich wohl fühlte, und der gleiche Interessen wie er hatte — die Psychiatrie oder die Bäume und Pflanzen — war er ein Freund,

bei dem einem die Zeit nie lang werden konnte. Und in den Gesprächen mit ihm trat als ausserordentlich positive Eigenschaft ein tiefer und warmer Humor und echte Empfänglichkeit für Humor hervor. Es gab aber für ihn auch etwas, das den erwähnten Gegenständen voranging: die Kinder. Ich denke an einen Besuch mit meiner Familie in der Chefarztwohnung von Pitkaniemi. Die Kinder waren auf Wunsch mit dabei. Jetzt trat die Psychiatrie beiseite, und in dem weiten Treppenhaus der Wohnung spielten unermüdlich drei Spielgefährten — zwei kleine Mädchen und der stattliche prächtige Onkel, der Hausherr. Dieses Bild hat sich mir unauslöschlich eingeprägt, und ebenso entsinne ich mich aus späteren Zeiten, wie Mäkelä für von einem Schiwettlauf erzählte, den er seinen Sohn und dessen Klassenkameraden geplant und veranstaltet hatte.

Es kam eine Zeit, da er nach menschlichen Schwierigkeiten eine eigene glückliche Familie und eigene Kinder hatte. Und es scheint, als habe ihm auch dies dazu geholfen, sich immer mehr aufzuschliessen, in seiner Tätigkeit wie in seinem persönlichen Verhalten Fühlung auch mit den Menschen zu gewinnen. So konnte er immer mehr Menschen um sich sammeln, und dank auch diesen Eigenschaften errang er sich die zentrale Stellung, die ihm im Leben schliesslich auf seinem Gebiet gehörte.

Eine sichtlich grosse Befriedigung bedeutete es für Mäkelä, dass es ihm in den Tagen unseres Winterkrieges vergönnt war, als Vertreter der Medizinalverwaltung im Hauptquartier und in der Sanitätsabteilung des Wehrministeriums nachdrücklich an der Organisation der Sanitätsverhältnisse in unserem Lande mitzuwirken, so undankbar und schwierig dies auch oft war, und freudig übernahm er auch seinen Anteil nach dem Ausbruch des neuen Krieges. Indes sollte er dies nicht viele Wochen tun, bevor er, auf seinem Posten erschöpft, der Natur seinen Tribut entrichtete.

Die endogenen Anlagen, die uns in die Welt mitgegeben sind, schaffen die Grundlage für unseren Charakter, aber die exogenen, von aussen stammenden Faktoren gestalten diesen auch ihrerseits während unseres Lebens zur Persönlichkeit. Ich glaube nicht, dass selbst der hochstehende Genotyp Väinö Mäkeläs, sei-

ne grosse intellektuelle und sonstige Begabung, allein den in seltenem Grade positiven Phänotyp zu schaffen vermochte, den wir besonders in seinen letzten Jahren in ihm verkörpert sahen. Dazu trugen auch teilweise, wie ich darzulegen versucht habe, die äusseren Faktoren bei. Erst durch die infolge seines Charakters den meisten von uns unsichtbaren Kämpfe entwickelte er sich zu dem, der er bei seinem Hinscheiden als Persönlichkeit und als nicht nur äusserer, sondern auch wirklicher Leiter der Entwicklung der Irrenpflege in unserem Lande war. Und als sein Platz verwaiste, trat von ihm nicht nur ein Mensch ab, der tiefe Furchen auf dem Ackerfeld der psychiatrischen Kultur Finnlands gezogen und eine edle Saat in sie ausgestreut hatte, sondern auch eine fesselnde Persönlichkeit und ein überragender Mensch.

S. E. Donner.

ON THE BLOCKING TIME OF THE CORTICAL ALPHA RHYTHM IN CHILDREN

BY

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INTRODUCTION

The alpha rhythm dominates during rest, preferably in darkness (*Berger*, 1929, *Adrian* and *Matthews*, 1934, *Grass* and *Gibbs*, 1938), among the different frequencies to which the brain potentials tend to synchronize. In adults the alpha waves appear with a frequency of 10 per sec., varying within narrow limits from case to case (*e.g.* *Jasper* and *Andrews*, 1938, *Bernhard* and *Skoglund*, 1939 a). In children the alpha frequency is lower (*Berger*, 1932, *Davis* and *Davis*, 1936, *Durup* and *Fessard*, 1936, *Loomis* et al., 1936), and systematic investigations have proved it to be a function of age (*Lindsley*, 1936, *Smith*, 1937, *Bernhard* and *Skoglund*, 1939 a); at the age of 1 year it is about 5 per sec. and afterwards continues to rise in early childhood. In later youth it gradually approaches the adult value of 10 waves per sec.

Light stimuli, among others, cause abolition of the alpha frequency in a manner, schematically illustrated by the diagram in Fig. 1, which shows the action potential of the eye (*Erg.*), the alpha blocking and the motor response from *m. biceps* in a human subject whose eye was illuminated with a relatively strong light.

Previous investigations show (*Bernhard*, 1940) that the latency of the human *Erg.* is a function of light intensity (*cf.* in animals, *e.g.* *Adrian* and *Matthews*, 1927, *Granit*, 1933).

Similarly the latency for the alpha blocking (*Durup and Fessard, 1936, Cruikshank, 1937, Bernhard, 1940*) and the reaction time are functions of brightness which closely reflect the changes of the peripheral latency (*Bernhard, 1940*). According to *Bernhard*, the "postretinal time", calculated from the beginning of the Erg. to the blocking of the alpha frequency remains fairly

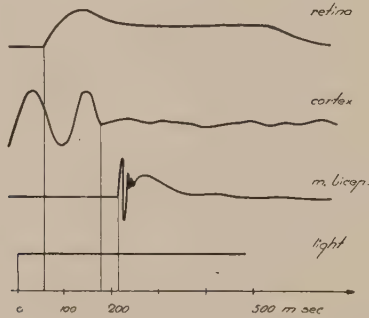


Fig. 1.

Diagram showing schematically the different responses from retina and cortex in relation to motor reaction (action potentials from right biceps) to light stimulus. Time in msec. (*Bernhard, Acta Physiol. Scand., 1940, 1 suppl. 1*).

constant at different intensities. This average "post. retinal" time, which obviously includes central events from the moment the excitation first reaches the cortex—in animals corresponding to the time for the "local cortical response" (see, *e.g., Bartley and Bishop, 1935*)—until the alpha frequency is blocked amounts in round figures to 100 msec. It may be of interest to note that this "central period" corresponds to the duration of an alpha wave, and just as the alpha waves in children are of longer duration than in adults (see above), so the blocking time for the alpha frequency is also longer for them (*Lindsley, 1938, Bernhard and Skoglund see Bernhard, 1940*). The experiments published below show the relation between the alpha-duration and the blocking time at different alpha frequencies; children of different ages have been subjects. In addition to this a correlation between the changes of the blocking and the reaction times in growth has been made, using earlier extensive reaction time measurements on children (*Morant and Koga, 1923*).

METHODS

For recording the human brain potentials a 4-stage push-pull coupled amplifier was used with a resistance capacity coupling at the input (giving a great time constant) in conjunction with a cathode ray oscillograph. Inter-stage coupling capacities were also used in order to eliminate frequencies above 20 per sec. The AG-AG Cl-electrodes were of the type previously described (see *Bernhard* and *Skoglund*, 1939 a). The leads were taken monopolarly, the active electrode being placed in the midline over the occipital region, while the other one, placed on *processus mastoideus*, served as indifferent electrode (see *Adrian* and *Matthews*, 1934 and *Rubin*, 1938).

During the experiment the subject lay in a sound-proof electrically shielded chamber, while the regulation of the light and recording were carried out in an adjacent room. These arrangements as well as the apparatus for the light stimuli have already been described in detail (*Bernhard*, 1939, part III).

Individuals ranging from $\frac{1}{2}$ to 25 years of age have been used as subjects.

RESULTS

A lively electrical activity from the brain is usually to be found in the early years of childhood—the first few months excepted—as compared with adults. This is partly because the potential waves are altogether of higher amplitude, and partly because there are more of them than in adults. But, as in adults, the alpha frequency is the dominant wave of the potential picture.

As a rule it is also found that the blocking of an existing alpha rhythm with light stimuli is less complete in children than in adults, especially with weaker stimuli. For this reason comparatively strong illumination has been used in our experiments. In order to create fairly uniform conditions we have, in analogy with previous experiments on blocking times in adults (*Bernhard*, 1940), chosen children with well pronounced dominant alpha frequency, suited to give a clearly marked blocking phenomenon. The blocking time has been calculated from the

onset of the light until cessation of the alpha rhythm (see fig. 2).

Fig. 2 shows the alpha blocking in a one-year-old and an adult of 25, at the same light intensity. These records as well as the values in Table 1 of the blocking time of 10 normal children of different ages show how the blocking time to a given

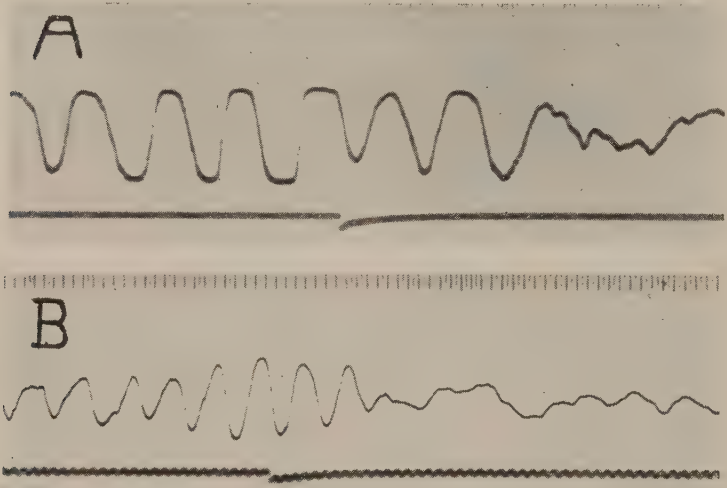


Fig. 2.

Oscillograph records showing the blocking by a given light stimulus of the occipital alpha rhythm in A, a one year-old child; and B, an adult of 25 years. Time in 1/100 sec.

intensity in children is generally lower than in adults, and also that the blocking time is longer the younger the child is. The relation between the blocking time and the alpha duration in the different cases will be seen from the index in the last column of the table, which gives the blocking time expressed in the number of alpha waves. As will be seen, the same value is to be found in all the cases, indicating a constant relation between the duration of the alpha waves and the blocking time.

Column II in Table 2 gives the averages found by us (1939 a) for the alpha frequency at different ages and column IV gives the averages calculated for the alpha duration. By using the

TABLE 1.

Case No.	Age years	Alpha per sec.	Alpha durat. in sec.	Blocking time in sec.	Index block. t/durat.
1	1	6.0	0.167	0.37	2.2
2	1	6.0	0.167	0.37	2.2
3	1	6.5	0.154	0.35	2.3
4	1	6.7	0.149	0.33	2.2
5	1	8.9	0.112	0.29	2.6
6	6	8.0	0.125	0.26	2.2
7	7	10.3	0.097	0.26	2.7
8	8	8.8	0.114	0.27	2.3
9	11	9.2	0.109	0.21	1.9
10	11	10.4	0.096	0.25	2.6
11	25	10.2	0.098	0.23	2.3
12	10	6.0	0.167	(0.38)	2.3
Average: 2.3*					

TABLE 2.

Age years	Average freq. alpha/sec.	Range alpha/sec.	Alphadurat. in sec.	Blocking time calculated in sec.
$1\frac{1}{2}$	5.3	3.5—6.6	0.189	0.43
2	6.5	5.5—7.4	0.154	0.35
4	7.4	6.2—8.9	0.135	0.31
6	8.3	7.5—9.2	0.121	0.28
8	8.5	7.5—10.3	0.118	0.27
10	8.8	7.5—10.2	0.114	0.26
12	9.3	8.4—10.4	0.108	0.25
14	9.3	8.2—11.1	0.108	0.25
$16\frac{1}{2}$	9.5	8.2—11.1	0.105	0.24
25	10.2	9.0—11.0	0.098	0.23

¹ The blocking time corresponds to 2.3 alpha-durations but if the peripheral latent period in the retina is subtracted, as was done in the work of *Bernhard* (1940) where the retinal electrical response was recorded simultaneously, the central blocking time or "post-retinal" time actually on an average corresponds to one full alpha-duration. Case 12 is a pathological case (see text).

experimentally obtained index value 2.3 for the light intensity tested (from Table 1) and the likewise experimentally obtained

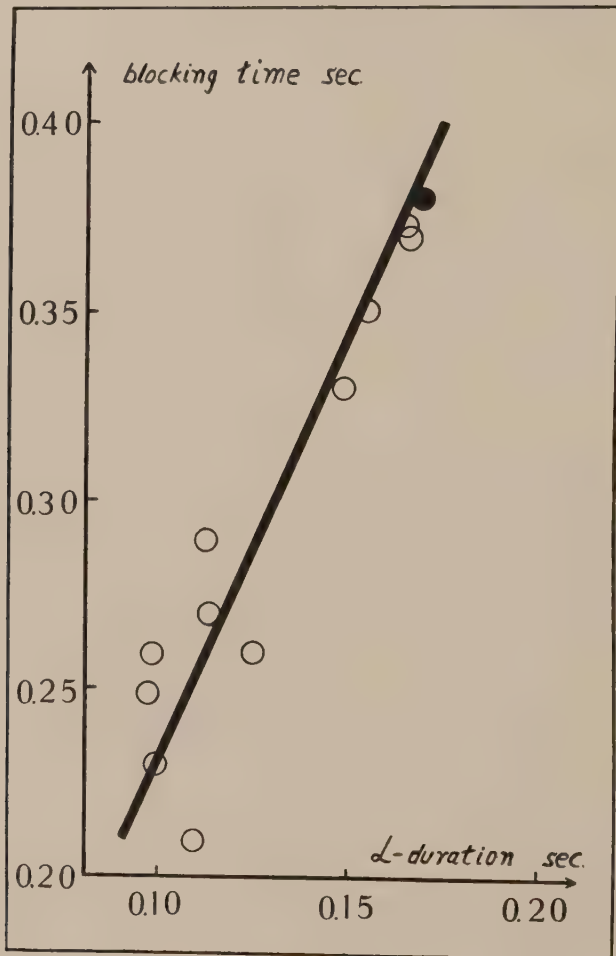


Fig. 3.

Plot of blocking time against alpha-duration. Straight line represents the averages calculated (column V in table 2) by using the index from table 1 and the values on alpha-duration in table 2. Open circles are the values obtained in the individual experiments on normal individuals (cases 1—11 in table 1). Filled circle is the value of blocking time in case 12 with

Debilitas psychica.

average values for the alpha duration (from table 2), the averages have been calculated for the blocking times that are to be expected at this light intensity at the different ages (Table 2, column V).

In Fig. 3, which graphically shows the relation between the

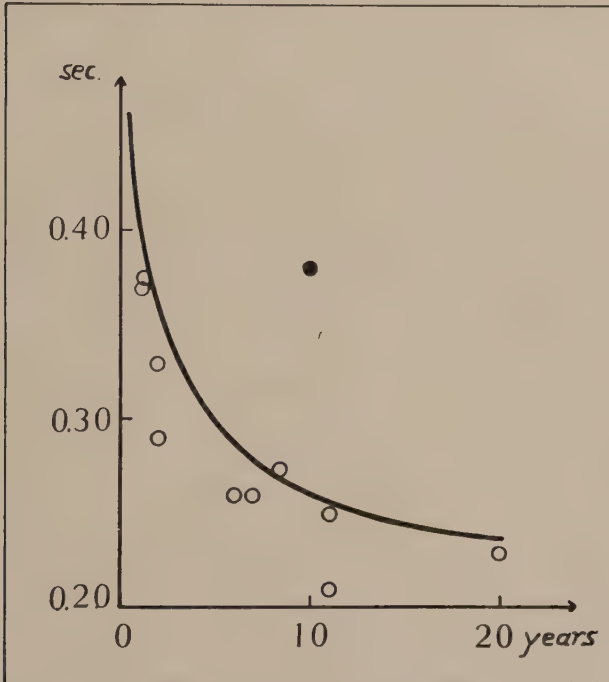


Fig. 4.

Plot of blocking time against age. The curve represents the averages from table 2. Open circles and filled circle as in fig. 2.

blocking time and the alpha duration at the light intensity used, these averaged values are represented by the straight line. As will be noticed, the values obtained in the individual experiments are grouped round this line, which illustrates the relation already referred to, *i.e.*, that the blocking time is proportional to the alpha duration. From this it follows that the blocking time as well as the alpha duration is to be regarded as a func-

tion of age, as is illustrated by the curve in Fig. 4, which represents the values of the blocking time calculated (from Table 2, column IV) in relation to age. It will be seen that the actual values obtained do not deviate much from this theoretical curve. The significance of the deviation, that does occur, will be discussed below.

According to previous experiments (*Bernhard and Skoglund*, 1939 b), certain cases of cerebral deficiency show a remarkably low alpha frequency in relation to age. In one case of serious *Debilitas psychica* (Case 12 in Table 1) the alpha frequency is far below the normal limit in corresponding ages. It is of interest to see that the blocking time in this case also is lengthened in proportion to the long alpha duration (index about 2.3). In this case, however, the value of the blocking time fits the blocking time-duration curve in Fig. 3 (filled circle), whereas it by no means corresponds to the blocking time-age function (filled circle in Fig. 4).

DISCUSSION

The results show how the latency for the alpha blocking by light shortens with increasing age to reach the minimum value of the adult during youth. If the blocking time is correlated to the alpha duration at the various ages, it will be seen that the former shortens with age in linear proportion to the duration of the alpha waves. Extensive experiments carried out at the Galton Laboratory on the reaction time for different stimuli and tabulated by *Morant and Koga* (1923), show that the shortening of the latency for those responses, which are released from the centre is of central origin. A correlation of our observations of the blocking time with *Morant and Koga's* conclusions as regards the reaction time indicates that the lengthening of the blocking time in children is a central phenomenon.

The course of the curve for the shortening of the blocking time with age can thus be said to apply to the central period of the blocking time. This means that the possible changes which the latencies of the peripheral processes (in the retina and optic

nerve) undergo with increasing age are in this connexion of negligible magnitude.

The question then arises whether a functional connexion really does exist between the central period of the blocking time (see above) and the alpha duration, or whether they are two variables, which are independently related to age. Our observations cannot definitely answer this question, although some factors indicate a direct connexion between the alpha duration and the central period of the blocking time. Thus, a comparison between Figs. 3 and 4 show that the experimentally obtained blocking values better agree with the average values relative to the alpha duration, whereas, when plotted against time, they show greater deviation from the average curve. The greater variations in the latter case are just what are to be expected if the blocking time is a function of alpha duration and they are then due to the obvious individual variations of the alpha frequency in every age group (see Table 2, column III). The case of cerebral deficiency also supports a direct connexion between alpha duration and blocking time which is seen from a comparison between Figs. 3 and 4, the results thus emphasizing the point that the alpha frequency may be an index for the speed of the central processes.

A comparison between the curve representing the shortening of the blocking time with age and the curve for the shortening of the reaction time with age is of a certain interest in this connexion. The absolute values are of no significance. Therefore, as both blocking time and reaction time reach a final minimum at about an age of 25, this minimum in both cases has been subtracted from the corresponding values at lower ages. These differences have then been plotted as ordinates instead of the absolute values. Fig. 5 gives the course of these curves. The curve for the shortening of the blocking time (1) is from Fig. 4, while the curve for the reaction time (2) is based on *Morant* and *Koga's* (1923) material on the reaction time for light in children.

According to *Bernhard* (1940 III) the moment of perception of light is at a constant interval from the beginning of the

blocking. Curve 1 may therefore be said to represent the course of the shortening of the perception process during the years of infancy, and, as will be noticed, the rapid development of the process takes place during the first two years of infancy, to which the markedly falling phase of the curve from "infinitely high" values to its asymptotic bend belongs. The corresponding

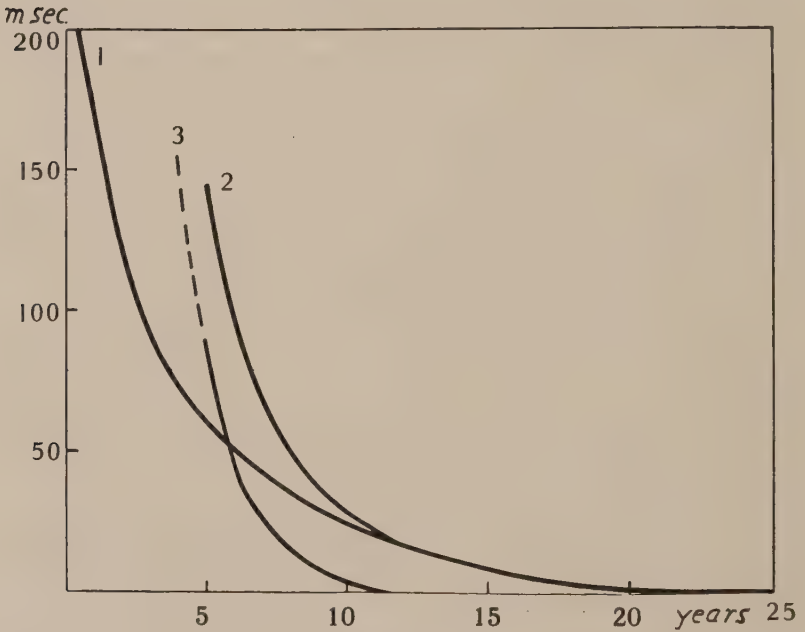


Fig. 5.

Diagram showing the curves for the shortening of the blocking time (1) and the reaction time (2) for light-stimuli in children. The differences between the final minimum values at 25 years of blocking time and reaction time has been subtracted from the values at lower ages in both cases and are plotted as ordinates in msec.

Curve 3 shows the difference between 2 and 1.

phase in the reaction time curve, on the other hand, is clearly shifted to a somewhat later age, and the two curves do not take the same direction until the age of 9 or 10. This shift must obviously be due to the central processes in the brain somewhere between the sensory input and the motor output. Their shorten-

ing takes place later than the development of the perception process. It is not likely that the latency for the peripheral sensory (retina and optic nerve) and motor processes (motor nerves and muscles) undergo any lengthening of a magnitude that influences these values (see *Bernhard*, 1940). Under this assumption the difference curve (3) between curves 1 and 2 represents the course of the shortening which the central processes undergo. The difference curve thus definitely gives an expression for the functional development of as yet unknown higher central processes.

SUMMARY

The blocking of the alpha-rhythm of the brain potentials caused by stimulation with light has been studied in children of different ages.

Recording instruments have been cathode ray oscillograph and condenser coupled amplifier.

The blocking time has been shown to be a function of the duration of the alpha-waves. It shortens during the growth period with increasing age in exact proportion to the shortening of the duration of the alpha-wave.

This shortening appears to be of central origin, and the relation between blocking time and alpha-duration indicates that the alpha-frequency is a measure of the speed of as yet unknown central processes.

The curve for the shortening of the reaction time with age have been compared with the corresponding curve for the shortening of the blocking time and discussed.

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THE CEREBELLAR CONNECTIONS OF THE NUCLEUS RETICULARIS LATERALIS (NUCLEUS FUNICULI LATERALIS) IN RABBIT AND CAT. EXPERIMENTAL INVESTIGATIONS

BY

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INTRODUCTION

The nucleus reticularis lateralis (syn. nucleus funiculi lateralis, nucleus lateralis oblongatae, nucleus lateralis anterior, nucleus lateralis medullae) belongs to those nuclei of the brain stem to which comparatively little interest has been paid. Its afferent and efferent connections are still only unsufficiently known.

¹ This research work was carried out with the aid of a grant from the Rockefeller Foundation to the Anatomical Institute, University of Oslo, and by grants from Nansenfondet.

At present apparently it is generally accepted that the efferent connections of this nucleus are with the cerebellum, and that the fibers travel through the homolateral restiform body. Extirpation of the cerebellum is followed by atrophy and loss of cells in the nucleus reticularis lateralis, as demonstrated by several early investigators (*Gudden* 1882, *Vejas* 1885, *v. Monakow* 1891, *Yagita* 1906, *Winkler* 1927 a. o.). Some authors hold that the connection is only homolateral (*Vejas*, *v. Monakow*), whereas others based on findings after section of the restiform body or extirpation of one half of the cerebellum conclude that the connections are partly crossed (*van Gehuchten* 1904, *Yagita* 1906 [dog, predominantly homolateral fibers]). Recently *Blakeslee*, *Freiman* and *Barrera* (1938) have confirmed in the monkey (macacus) that section of the restiform body or extirpation of the cerebellum after some time is followed by a practically total loss of cells in the homolateral nucleus reticularis lateralis. As far as can be seen, however, no experiments have as yet been recorded, demonstrating which part of the cerebellum is the end station of the fibers from the nucleus reticularis lateralis. *Ziehen* (1934) regards it probable that the fibers terminate in the vermis. From the findings in cases of cerebellar atrophy and cerebellar malformation some authors have pointed out special divisions of the cerebellum as the end stations of the fibers. *Brun* (1925-26), for instance, assumes that the flocculus receives the fibers derived from the magno-cellular lateral portion of the nucleus, and previously he has regarded it probable that the medial part of the nucleus sends its fibers to the medial divisions of the cerebellum, the lateral to the lateral divisions (1917-18). Judging from his studies of cerebellar malformations, *Marburg* (1924) states, that the fibers end in the "lobi laterales".

Concerning the afferent fibers to the nucleus reticularis lateralis our knowledge is likewise incomplete. After hemisection of the spinal cord in newborn animals the nucleus on the same side becomes atrophic (*v. Monakow* 1883). From the fibers in the antero-lateral column collaterals are given off to the nucleus (*Cajal* 1909 et al.), and in Marchi-preparations fibers in the dorsal (*Lewandowsky* 1904, *Mac Nalty* and *Horsley* 1909,

Blakeslee, Freiman and Barrera 1938 et al.) and in the ventral spino-cerebellar tracts (*Collier and Buzzard 1903, Lewandowsky 1904, Blakeslee, Freiman and Barrera 1938 a. o.*) have been seen entering the nucleus and probably ending there or giving off collaterals. In addition to these fibers some authors have described a small amount of fibers from the posterior funiculi to the nucleus reticularis lateralis (*Marburg 1924, Blakeslee, Freiman and Barrera 1938 et al.*). The statement of some early authors (*Thomas, Orestano*) that cerebellofugal fibers reach the nucleus via the restiform body, must probably be regarded as disproved by the negative findings of several authors who have studied the efferent projections from the cerebellum by severing the inferior cerebellar peduncle or by injuring the cerebellum and its nuclei (v. e.g. *Allen 1924, Jansen and Brodal 1940, 1942*).

The question of the exact termination of the fibers from the nucleus lateralis medullae within the cerebellum has gained new interest after the recent advances in the comparative anatomy of the cerebellum (investigations of *Herrick et al.* and especially of *Larsell*) and the newer results of studies of the cerebellar connections. According to these recent investigations the cerebellum can be regarded as consisting primarily of two parts: a phylogenetically old lobus flocculo-nodularis (*Larsell*) with predominantly vestibular connections (*Ingvar 1918, Dow 1936, 1938*) and a younger part, the corpus cerebelli (*Herrick, Larsell*) with spino-cerebellar and pontine afferents. Within the corpus cerebelli the older divisions, the lobus anterior and the pyramis and uvula (lob. c_1 and lob. b of *Bolk*), are the end stations of the spino-cerebellar tracts (*Mac Nalty and Horsley 1909, Ingvar 1918, Beck 1927, Jansen 1931, Brodal and Jansen in man 1941*). Previously I have brought forward evidence that the fibers from the nucleus cuneatus externus (nucleus Monakow) are distributed to the same regions of the cerebellar cortex as the spino-cerebellar fibers (*Brodal 1941*). The younger parts of the corpus cerebelli, the lobulus medius medianus (*Ingvar, lobulus c_2 Bolk*) and the lobulus anso-paramedianus, forming together the neo-cerebellum, receive by far the most if not all

of the ponto-cerebellar fibers (*Borowiecki* 1911, *Masuda* 1914, *Winkler* 1927, *Sunderland* 1940). The position of the paraflocculus is still uncertain.

From the fact that the nucleus reticularis lateralis receives spino-cerebellar fibers or at least collaterals from them, it appears a priori probable that the efferent fibers of the nucleus reach the lobus anterior and the pyramis and uvula. However, the peculiar architecture of the nucleus, composed as it is of parts differing in structure, might reasonably be interpreted as an indication of different connections of the separate parts. The program of the present investigations was then to try, if possible, to determine:

1. *To which part of the cerebellum are the fibers from the nucleus reticularis lateralis distributed?*

and eventually:

2. *If all of the fibers do not pass to the same parts of the cerebellum, is there any correlation between different parts of the nucleus and the corresponding terminal areas in the cerebellum?*

By means of a modified *Gudden* method, to be briefly described below, it seemed possible to study these fiber connections, as this method has yielded good results in experimental investigations of the olivo-cerebellar connections (*Brodal* 1940c) and of the cerebellar connections of the nucleus cuneatus externus (*Brodal* 1941).

MATERIAL AND METHODS

The experiments were performed on rabbits and cats. Under ether anaesthesia circumscribed lesions were made in different parts of the cerebellum, and the distribution of the ensuing retrograde cellular changes in the nucleus reticularis lateralis were studied. 137 rabbits and 87 cats were used, for the most part the same animals as were employed for a study of the olivo-cerebellar localization (1940c) and the cerebellar connections of the nucleus cuneatus externus (1941). Several of the animals, however, died too soon to be of any use, and in others

the lesion turned out to be less circumscribed than intended or there were accessory lesions that spoiled the series.

The cerebellum and the brain stem after the killing of the animals were fixed in alcohol, embedded in paraffin, sectioned serially (sections of 15 μ thickness) and stained with thionin. A detailed description of the methods employed and a discussion of the difficulties involved in determining the site of the lesion exactly is given in the paper on the olivo-cerebellar localization (*Brodal* 1940c), to which the reader is referred in regard to details. Below only a brief outline of the modified *Gudden* method as introduced by the author (*Brodal* 1939, 1940a) will be presented.

By this modification of the *Gudden* method the animals are operated upon at an age of 8-20 days (eventually somewhat more for the cats) and they are killed usually after 6-12 days. By this method one has the advantage that the animals' resistance to the operative trauma is greater than when they are operated immediately after birth, and by killing them already few days after the lesion has been made, the secondary shrinking is avoided which otherwise will develop and make the evaluation of the changes difficult. In addition the changes in the affected nuclear masses are far more clear-cut than they are after corresponding lesions in adult animals, especially because all nerve-cells affected by retrograde changes tend to disappear within a few days, whereas in adult animals part of the cells will not disintegrate acutely but atrophy slowly. The evaluation of an eventual cell-loss is far less difficult than in adult animals, because the cells in the young animals lie far more densely packed. Furthermore the picture of the acute retrograde cell changes is more characteristic in newborn animals than in adults, and the glial reaction is more pronounced. For these reasons the changed areas can be more easily identified. A short description of the cellular changes illustrating these features will be given below.

In presenting the material use will be made of diagrams of the cerebellum and of the nucleus reticularis lateralis. The diagrams of the cerebellum of the rabbit and the cat, representing the cerebellar surface as imagined unfolded in one plane, are the same as those employed in previous publications (the diagram of the rabbit's cerebellum is also published in an atlas of this organ, *Brodal* (1940b)). The diagrams of the nucleus reticularis lateralis (figures 1 and 2) are drawn by means of a projection apparatus, with equal intervals between the sections reproduced. The lesion is indicated by solid black where the

cerebellar surface is totally destroyed or removed, by hatchings where the lesion is more superficial. Areas, the fibers to which have been cut, are stippled. In the diagrams of the nucleus reticularis lateralis areas with the most intense changes, where most of the nerve cells are changed or have disappeared, are indicated by solid black. Lesser degrees of cell loss or cellular changes are indicated by hatchings, simple hatchings where slight, crossed hatchings where more intense.

Normal anatomy of the nucleus reticularis lateralis.

In the literature descriptions are to be found of the normal anatomy of the nucleus reticularis lateralis in the rabbit and the cat (Cajal 1909, Winkler and Potter 1911, 1914), in the monkey (Blakeslee, Freiman and Barrera 1938) and in man (Jacobsohn 1909, Fuse and v. Monakow 1916, Brun 1917-18, Gagel and Bodechtel 1930, Mingazzini 1934 and others). However, the various descriptions are partly divergent, and especially the subdivisions of the nucleus proposed by the different authors do not quite conform for the various species described. On this account it is difficult to make comparisons, and as the descriptions as a rule are only fragmentary, no conclusions concerning the relative development of the different subdivisions of the nucleus can be drawn from the available data.

So a description of the nucleus in the animals used in the experiments to be reported, *i.e.*, rabbits 2-3 weeks old and cats 3-4 weeks old, may be appropriate and is given here.

The nucleus reticularis lateralis in the rabbit (Fig. 1) extends in the caudo-rostral direction from a level slightly below the caudal pole of the inferior olive (medial accessory olive) to a level somewhat caudal to the rostral pole of the olivary complex. The caudal pole of the nucleus is well defined and rather sharply circumscribed, whereas the rostral end is less definite, consisting of a rather diffusely limited portion. This rostral end extends for a longer or shorter length rostrally, disappearing gradually and showing considerable individual variations.

The nucleus reticularis lateralis may somewhat arbitrarily be subdivided in a *large-celled portion* and a *small-celled portion*, which in some places are rather sharply separated from each other, in other places

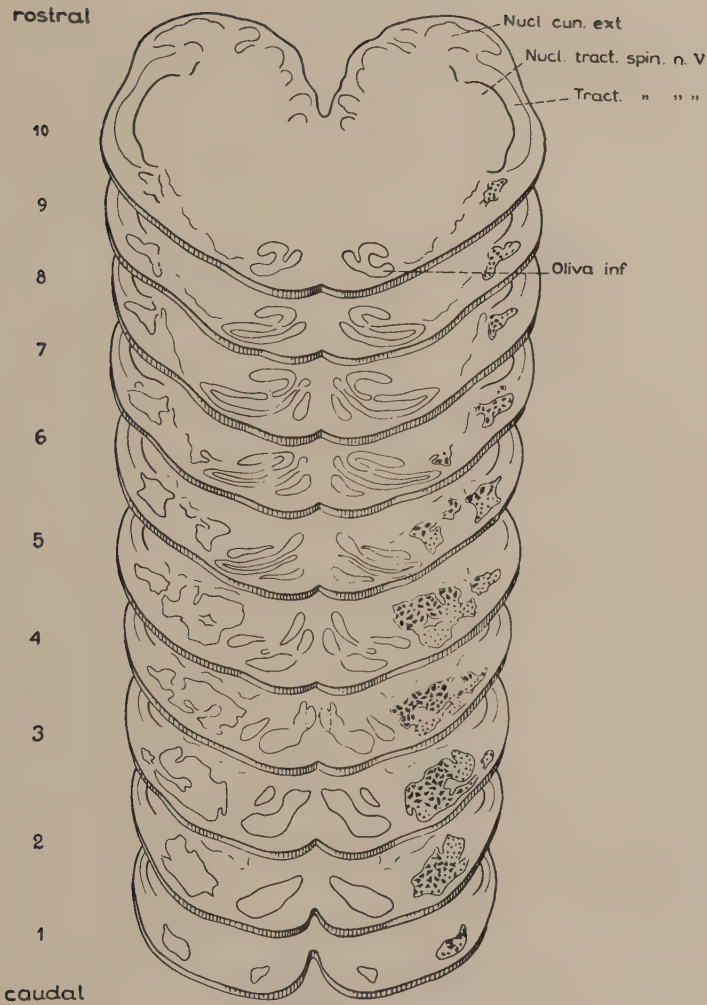


Fig. 1.

Diagram of the nucleus reticularis lateralis in the rabbit. On the right side of the diagram the cell types predominant in the different parts of the nucleus are presented diagrammatically.

however fuse without distinct borders, and a rostral, *subtrigeminal portion*. In Figure 1 the type of cells predominantly present is indicated by larger or smaller dots.

The magno-cellular portion forms the greater mass of the nucleus. It begins at the caudal pole of the nucleus (section 1 in Fig. 1), and reaches its largest size at the level of sections 3-5. The rather massive caudal half of the nucleus is largely formed by this magno-cellular portion which is composed of predominantly large cells, multipolar, stellate or more seldom pear-shaped, with rather coarse Nissl-granules. The cells have an approximately centrally placed nucleus with a distinct nucleolus (vide Fig. 3, n_1).

Besides these cells there are in the magno-cellular portion scattered cells of the small and medium-sized type, to be described below, especially at the transitory regions to the parvi-cellular portion. The cells are arranged in small groups and clusters separated by strands of fibers, giving the nucleus a reticular appearance (v. Fig. 5 b). Passing rostralward from section 5 in Fig. 1, the magnocellular portion of the nucleus becomes subdivided into two parts, a medial and a lateral (section 6). Of these the medial division disappears approximately at level 7, sometimes somewhat more rostrally, whereas the smaller lateral division ends approximately at the level of section 6.

The parvi-cellular portion of the nucleus also makes its appearance at the caudal pole of the nucleus, at this level fusing with the more dorsally and medially placed magno-cellular portion. Farther rostrally this parvi-cellular portion forms a sort of cap on the lateral and ventral surface of the magnocellular portion (sections 2-5 in Fig. 1) and is partly separated from it by a cell-free narrow zone, partly fusing with it, as indicated in Fig. 1. The rostral end of the parvi-cellular portion is found ventral to the medial part of the magno-cellular portion at the level of section 6.

The cells of the parvi-cellular portion are partly of medium size of the type pictured in Fig. 3 (n_2), partly very small, consisting only of a small clear nucleus with a nucleolus, surrounded by a scanty amount of cytoplasm containing very fine, sparse Nissl-granules (Fig. 3, n_4). Occasionally also a cell of the largest type can be seen (Fig. 3, n_1). Also this parvicellular portion is loosely structured, the cells for the most part lying rather far apart.

The subtrigeminal portion forms a rather well characterized division of the nucleus, constituting alone the rostral part of it. As previously mentioned this part shows considerable individual variations and often extends somewhat farther rostrally than in the diagram in Fig. 1. It is situated immediately ventral to the nucleus and tractus spinalis nervi V, and in some places scattered cells often connect these two nuclei. Caudally the subtrigeminal portion fuses with the other divisions to some extent and no distinct caudal limit can be fixed for this portion. At the level of section 6 in the diagram it is more or less continuous with the lateral part of the magno-cellular portion dorsally, and farther caudally it is

continuous with the rostral part of the parvi-cellular portion (levels 4-5 in the diagram). The most lateral part of the nucleus reticularis lateralis at levels 5 and farther caudally should probably be considered belonging to the parvi-cellular portion. Also the cellular structure gives evidence of the transition between these parts, as most of the cells found in the caudal part of the subtrigeminal portion (level 6-5), especially ventrally, are of the same types as those met with in the parvi-cellular portion. When, passing rostralwards, the subtrigeminal portion proper (section 7-10) is reached the structure gradually undergoes a change. The cells lie farther apart, more so at the rostral levels, and also the type of cells differs. Many of the cells are of a medium size (vide Fig. 3, n₃), generally piriform or rounded, with finer Nissl-granules than in the large cells of the magno-cellular portion, and the nucleus is more often placed somewhat excentrically. Between these cells, however, not few cells of the smallest type and scattered cells of the largest type are also encountered.

At most places the limits of the nucleus reticularis lateralis towards the surrounding structures can be clearly determined. Only at the levels where the medial division of the magno-cellular portion disappears rostrally, (section 7 in the diagram) is there often no distinct cell-free zone between the nucleus and the substantia reticularis, and the determination of the exact limit at this place is somewhat arbitrary.

The description given above refers to the findings in animals 14-20 days old. In adult animals the cells lie considerably more scattered, but apart from this, conditions are similar. The description conforms in general to that given by *Cajal* (1909). The magno-cellular portion corresponds to his *noyau interne ou principal*, the parvi-cellular portion to his *noyau postérieur ou externe*. The small division of the nucleus which *Cajal* describes as *foyer linéaire*, lying laterally and seen only in a few sections, cannot in all instances be isolated as a separate part. When present it is found approximately corresponding to level 5 of the diagram. Judging from *Cajal's* drawing and description, it is certainly not identical with the part designated the subtrigeminal portion above, but should, as *Cajal* himself mentions, probably be considered as belonging to the parvi-cellular portion. Apparently the subtrigeminal portion was not included in the nucleus reticularis lateralis by *Cajal*, but the fact that this cell group shows changes after lesions of the cerebellum corresponding to those of the other divisions (cf. later), indicates that it should certainly be considered part of the nucleus. In the *Wink-*

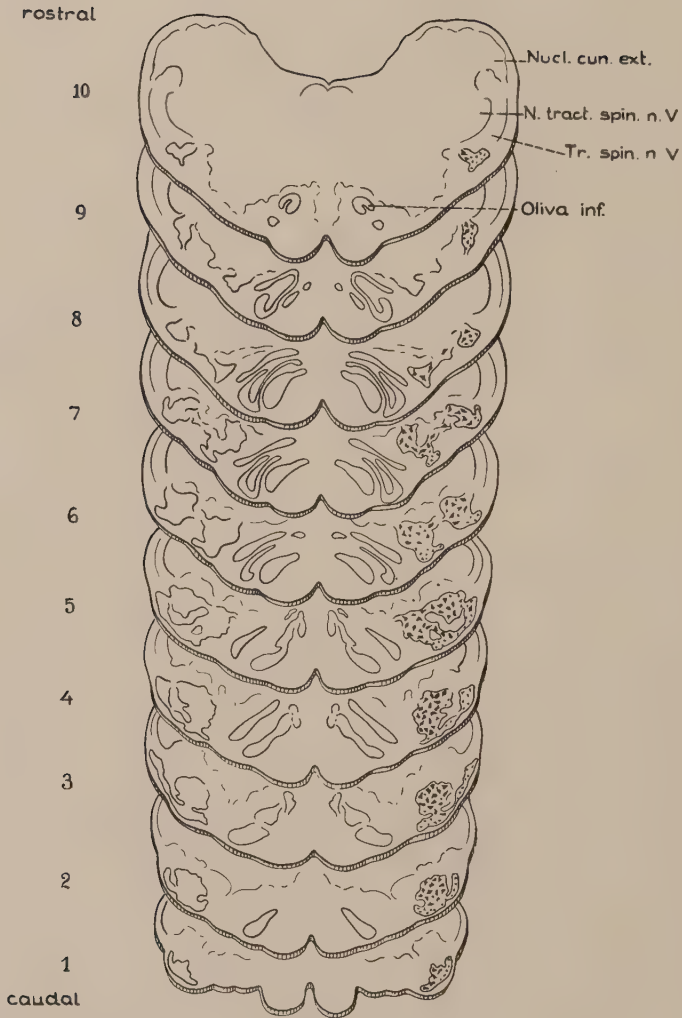


Fig. 2.

Diagram of the nucleus reticularis lateralis in the cat after the same principle as in Fig. 1.

ler and *Potter* atlases no details concerning the architecture of the nucleus are mentioned.

A comparison between the nucleus reticularis lateralis in the experimental animals and the nucleus in man is difficult

on the basis of the descriptions found in the literature. The portion of the nucleus which in man is designated the nucleus infratrigeminalis (*Jacobsohn, Gagel and Bodechtel*) or "Quintus-Anteil" (*Fuse and Monakow*) probably corresponds to the subtrigeminal portion in the rabbit and the cat, which differs structurally in some points from the rest of the nucleus. The magno-cellular portion probably corresponds to at least part of the magno-cellular "Haupt-portion" of *Fuse* and *v. Monakow* and to the part called nucleus lateralis internus by *Ziehen*.

The nucleus reticularis lateralis in the cat is very similar to that of the rabbit, both in regard to its cellular structure and subdivisions. On this account a detailed description is regarded as superfluous. The reader is referred to the diagram in Fig. 2. The nucleus in the cat appears somewhat more massive and comparatively larger than in the rabbit.

The retrograde cell-changes in the nucleus reticularis lateralis.

Fig. 3 gives some drawings of representative stages in the retrograde changes seen in the cells of the nucleus reticularis lateralis after lesions of the cerebellum in rabbits 8-20 days old at the time of operation.

In general the retrograde changes in the cells of the nucleus reticularis lateralis show great conformity with the corresponding changes in the cells of the inferior olive and the nucleus cuneatus externus, as they have been described previously (*Brodal 1939, 1941*). The cytological changes are best seen in the large cells of the magno-cellular portion of the nucleus, but also in the middle-sized cells the main points can be made out relatively easily. The smallest cell type, on the other hand, offers considerable difficulties in regard to finer cytological studies, mainly on account of its scanty mass of cytoplasm and the normally small and sparse Nissl-granules.

As early as 4 days after a rather extensive injury to the cerebellum many of the large cells in the magno-cellular portion of the nucleus reticularis lateralis show a nearly fully developed picture of the acute retrograde changes, the retrograde reaction (corresponding to *Nissl's* "Primäre Reizung" in the peripheral motor neurons). The tigroid granules for the most part have disappeared (Fig. 3, r_1), only near the periphery of the cells some smaller granules remain. The rest of the cytoplasm has as-

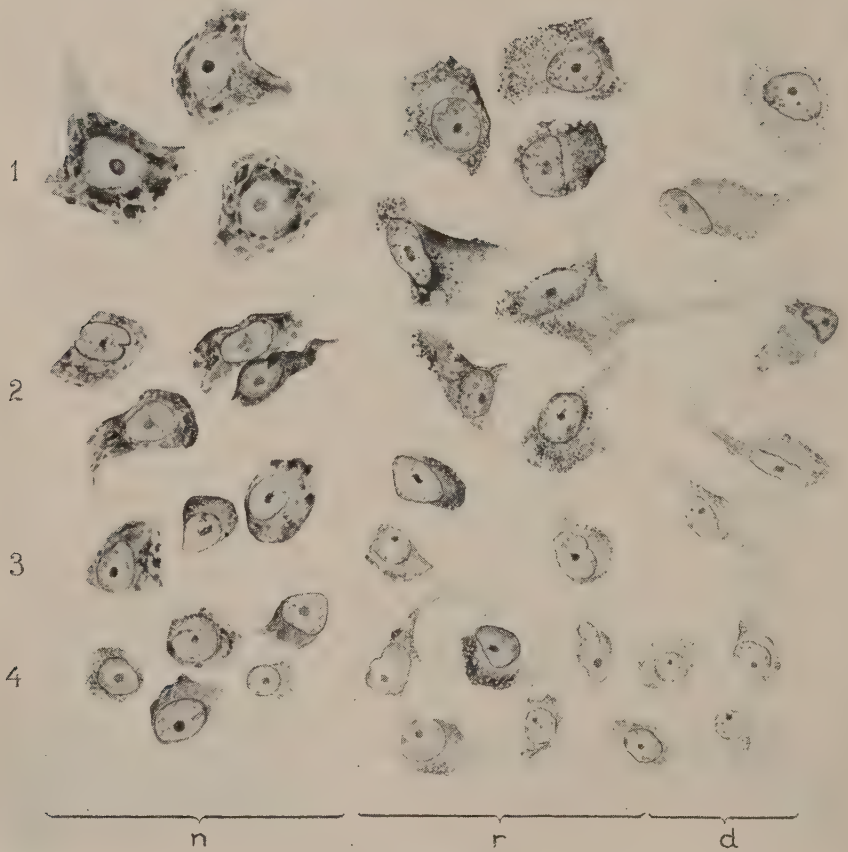


Fig. 3.

Drawings of the different cell types (1, 2, 3, 4) of the nucleus reticularis lateralis of the rabbit (2-3 weeks old) and the retrograde changes in these cells. n: normal cells; r: cells in early stages of the retrograde reaction; d: cells in late stages, partly disintegrating. 1: Cells forming the largest mass in the magno-cellular portion of the nucleus, 2: Cells of the type found predominantly in the parvi-cellular portion, 3: The medium-sized and larger cells found in the rostral, subtrigeminal, portion of the nucleus, 4: The smallest cell type seen in the parvi-cellular portion and scattered between the other types throughout the entire nucleus. Cf. text.

(Leitz oil imm. 1.12, Oc. 5, reduc. Magnif. $\times 525$.)

sumed a diffuse, lighter bluish colour, appearing more or less "laked", sometimes showing also small vacuoles. The contours of the cells are changed, the cells often appear more rounded, have partially lost their previously polygonal appearance, and the cell-size is somewhat reduced. The nucleus is no longer found in the center of the cell, but characteristically lies distinctly peripherally, close to the cell membrane. Besides these fully developed pictures other cells are seen, showing the same changes to a lesser degree. Obviously these are cells in an earlier stage of the retrograde changes. At later stages, approximately from the 6th day after the operation, a loss of cells is to be noted in the nucleus, and as well as cells still showing the picture of the fully developed retrograde changes described above others are found in a more advanced degree of cellular change, obviously in the process of disintegration (d_1 in Fig. 3). The cytoplasm is practically devoid of Nissl-granules and appears only as a light bluish zone on one side of the clear nucleus with the diminished nucleolus. The borders of the cells are often quite indistinct and in still more advanced stages the nuclear border cannot be definitely made out in all places. Cells of this type on account of their paleness are apt to be overlooked when the section is examined with low power magnification.

Approximately 8-10 days after the operation there is found a loss of cells in the nucleus reticularis lateralis [the degree of which is dependent on the size of the injury (cf. below)]. The remaining cells appear to be normal, (only a few cells with retrograde changes still being present). This probably means that all those cells which are affected with the retrograde changes disappear by dissolution during the first 8-10 days after the injury, in close analogy to the findings in the inferior olive.

The medium-sized cells for the most part found in the parvi-cellular portion show changes corresponding to those described. Characteristic pictures of this type of cells and its changes are shown in Fig. 3, r_2 , d_2 from the parvi-cellular portion, r_3 , d_3 from the subtrigeminal portion. The cells of these types also become somewhat diminished, tigrolysis appears, beginning centrally, and the nucleus moves to the periphery of the cell and likewise is diminished. Later these cells also disintegrate.

In regard to the *smallest cells* of the nucleus, predominantly found in the parvi-cellular portion, it cannot always be determined with certainty whether a single cell of this type is normal or not. When, however, a larger part of the nucleus is changed, and the site of the changes can thus be determined, it is seen that the small cells appear still lighter than normal, the normally scanty cytoplasm being practically free of Nissl-substance (Fig. 3, r_4 , d_4). The amount of cytoplasm appears reduced. As the nucleus is normally situated close to the periphery of the cell, no shifting in its position can be ascertained.

A glial increase accompanies these changes in the nerve cells. When a considerable amount of the nerve cells in a part of the nucleus is

changed the glial increase and the signs of glial "activation" are distinct, when only few cells are changed the glial reaction is less definite.

The retrograde cell changes in the cat correspond to those seen in the rabbit and a detailed description is considered superfluous.

Remarks on the evaluation of the retrograde changes found in the nucleus reticularis lateralis after cerebellar lesions.

It goes without saying that the determination of a partial loss of cells in a nuclear mass is far more easy where the projection-system in question shows a highly organized spatial localization, than where the projection is more or less diffuse. Thus in the inferior olive it is possible to determine a rather small area affected with a loss of cells resulting from a small injury in the cerebellum, since the olivo-cerebellar projection is characterized by a well developed spatial localization. As will be demonstrated below, the projection of the nucleus reticularis lateralis on the cerebellum shows only a very slight degree of localization, and lesions in different parts of the cerebellum (e.g. the vermal region and the "hemispheres") to a great extent are followed by cellular changes in the same regions of the nuclear complex. In most instances, therefore, small injuries will give no conclusive results.¹ Especially it will not be possible to define exact borders for the projection areas of the different cerebellar subdivisions. Valuable aids in this respect may be gained where the animal has been killed so early that some cells are still present in the acute retrograde stages, as these cells can often be identified rather easily.

In the nucleus reticularis lateralis, however, another feature tends further to give difficulties, namely: the composition of the nucleus of several parts varying normally in regard to the density of the cells and the type of cells predominantly present, as described above. The parvi-cellular portion, with its cells lying normally rather far apart offers considerable difficulties

¹ Accordingly many of the series which were useful for the study of the olivo-cerebellar connections were without value in the present investigation.

in his respect. Still more is this the case in the rostral extension of the nucleus (the subtrigeminal portion) where the few cells lie rather scattered and where the individual variations are considerable. The difficulties are further augmented by the small difference between the normal and the retrograde cells in this part as pictured in Figure 3. When only some or a moderate number of the cells in this portion have disappeared or show retrograde changes, doubt is often left as to the presence of changes. For these reasons great care has been taken to consider the nucleus as affected only when the changes are undisputable.

In spite of the above-mentioned difficulties encountered by the estimation of loss of cells and cellular changes in the nucleus reticularis lateralis, it has as a rule been possible to decide with certainty the presence of changes in the nucleus in experiments where the cerebellar injury is not too slight. A circumstance of great value in this determination is the fact that the projection in question is homolateral, so that comparison can be made with the normal nucleus of the other side in most instances where the lesion is unilateral. But in some instances, where the lesion is bilateral, this opportunity is lost. In such cases it is necessary to make the comparison with normal series from animals of a corresponding age, thus necessarily introducing a moment of uncertainty. Great care has therefore been taken in such series to record only clear-cut changes.

PRESENTATION OF MATERIAL

Below some representative series showing the organization of the projection of the nucleus reticularis lateralis on the cerebellum will be reported and partly illustrated.

A. Rabbits.

Division of the corpus restiforme is followed by a practically total loss of cells in the homolateral nucleus reticularis lateralis. Only scattered cells, one or two in every section, are left. This

confirms the findings of previous authors, and on this account the corresponding series (rabbit O.37, 10 days old at operation, killed after 9 days) will not be illustrated or reported in detail.¹

Series with partial injury to the cerebellum deserve far greater interest. The effects of injuries to the vermal portion of the cerebellum will first be dealt with.

Rabbit O.33, 16 days old at operation, killed after 15 days.

(Fig. 4.)

Injury: A paramedian incision was made in the cerebellum on the boundary between one cerebellar hemisphere and the vermis (indicated by a black stripe in Fig. 4). Penetrating the anterior lobe and the lobulus c the injury has reached the 4th ventricle ventrally. The rostral pole of the nucleus fastigii on the side of the lesion is slightly injured. As a consequence of the lesion all fibers passing to or from the vermal portion of the anterior lobe and the lobulus c are severed, and most of the fibers in connection with the lobulus b and a are likewise injured where they curve above the nucleus lateralis to reach these lobules. The area to which the fibers have been severed is indicated by stippling in Fig. 4.

In the *homolateral nucleus reticularis lateralis* a considerable loss of cells is found as indicated in the diagram of the nucleus in Fig. 4. The photo-micrograph in Fig. 5a shows the loss of cells corresponding approximately to section 3 in the diagram of the nucleus. (For comparison the normal nucleus on the other side is presented in Fig. 5b.) As will be seen from the diagram in Fig. 4 the most intense changes are located to the caudal and ventro-lateral parts of the nucleus, partly in the magnocellular but especially in the parvi-cellular portion (cf. the diagram in Figure 1). However, no part of the nucleus is quite normal, also the dorso-medial and rostral parts show a cell-loss of more moderate intensity. Most of the remaining cells are normal, only scattered cells in late stages

¹ Why a few cells in the nucleus do not disappear after division of the restiform body cannot be stated. From the sections it appears that a few fibers in the restiform body may have escaped destruction. However, the possibility also exists that some of the fibers from the nucleus pass to the vestibular nuclei (in analogy with the olivo-cerebellar fibers) or to the contralateral side of the cerebellum. Also other authors have described a few intact cells after section of the restiform body or hemidecerebellation, or even after complete extirpation of the cerebellum (Blakeslee, Freiman and Barrera). The latter circumstance points towards the vestibular nuclei (or other structures of the brain stem?) as the possible end-point for the fibers of these cells.

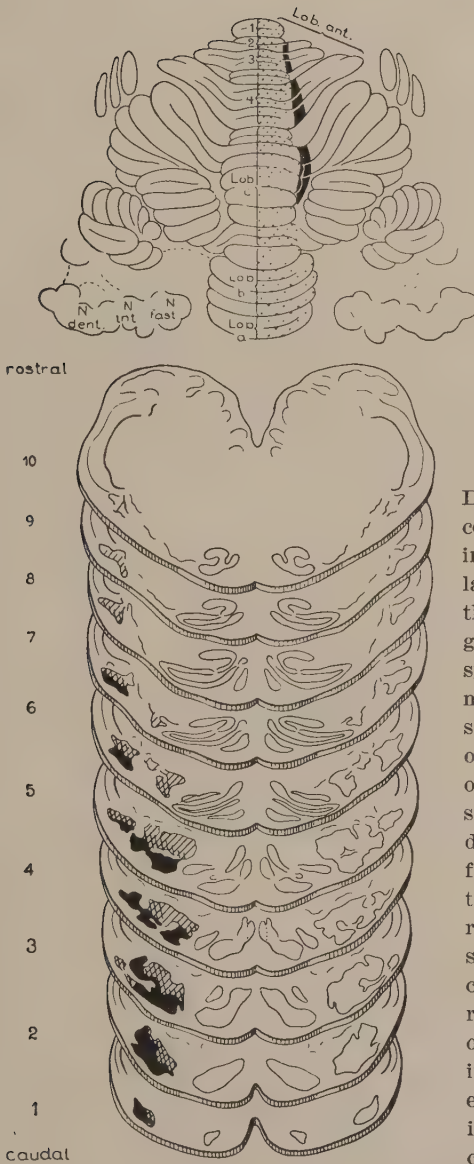


Fig. 4.

Diagram of the lesion in the cerebellum and the changes in the nucleus reticularis lateralis in rabbit O.33. In this and the following diagrams of the same type the symbols have the following meaning: In the cerebellum, solid black: areas removed or totally destroyed at the operation: hatched: more superficially injured regions; dotted: areas in which the fibers have been severed. In the nucleus reticularis lateralis, solid black: areas with severe loss of cells (not total cell-loss! cf. Fig. 5a) or retrograde changes in most of the cells; crossed hatchings: considerable but slighter changes; simple hatchings; slight but definite changes.

of retrograde changes and disintegration are to be found. In the most affected areas there is a considerable increase in the glia.

The findings in this experiment at once make it clear, that *the vermal region of the cerebellum receives not all but only part of the efferent fibers from the nucleus reticularis lateralis*. More than one half of the total cell mass of the nucleus has disap-

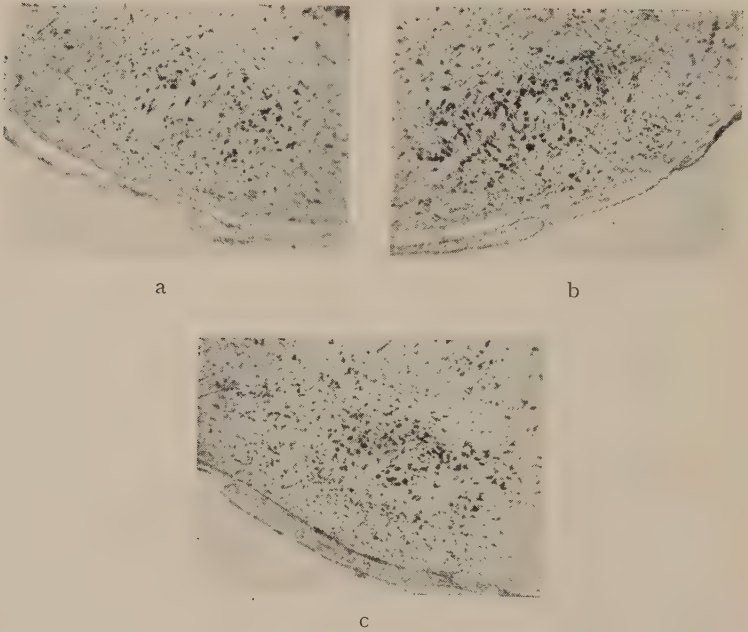


Fig. 5.

- a: Microphoto of the nucleus reticularis lateralis on the side of the lesion in rabbit O.33 approximately corresponding to section 3 in the diagram in Fig. 4.
- b: Normal nucleus contralateral to the lesion. The loss of cells in the nucleus homolateral to the lesion is evident.
- c: The changed nucleus in rabbit O.65 corresponding approximately to section 3 in Fig. 9 (compare with b). Magnif. $\times 16$.

peared. It is furthermore evident, that the *fibers to the vermal region arise from all parts of the nucleus, though predominantly from the caudal and especially the ventrolateral caudal parts,*

i.e. the *parvi-cellular portion*. Whether the nucleus fastigii also receives some fibers cannot be decided.

A corroboration of these findings is given by the following experiment.

Rabbit O.137, 10 days old at operation, killed after 8 days
(not illustrated).

Injury: With a tiny knife and a pincette the entire median part of the cerebellum (the vermal region) was removed. (A diagram of the lesion is found in my paper on the olivo-cerebellar localization, 1940, p. 71.) Also both fastigial nuclei are lost and the medial part of both nuclei interpositi is damaged. On the left side also the caudal folia of the paramedian lobule have disappeared. The lesion in the anterior lobe extends somewhat farther laterally than the vermis, strictly taken.

In *both nuclei reticulares laterales* a considerable loss of cells is found, occupying the same areas as indicated in the diagram from the previous series (Fig. 4). Also in this experiment the most intense changes are found in the caudal and ventro-lateral parts of the nucleus, i.e. predominantly in the *parvi-cellular portion*. There is a moderate increase in the glial elements, most intense in the areas affected with the heaviest cell-loss.

The findings in this series thus correspond very well with the conclusions reached on the basis of the previous experiment. However, neither experiment gives any information about which part of the "vermis" is the ending place of the fibers from the nucleus reticularis lateralis, or whether all of the vermis or only certain divisions receive these fibers, a question of considerable interest. The following experiments elucidate this problem.

Rabbit O.27, 10 days old at operation, killed after 7 days.
(Fig. 6.)

Injury: The left half of the lobulus c has been practically totally destroyed. Only the most caudal folia are left but are slightly damaged. The lesion also extends in some degree to the right half of the lobulus c. The nuclei are intact.

In *both nuclei reticulares laterales* changes are found, but only to a slight extent in the right. In the left nucleus some areas show a considerable loss of cells, although nowhere as intense as in the previous series,

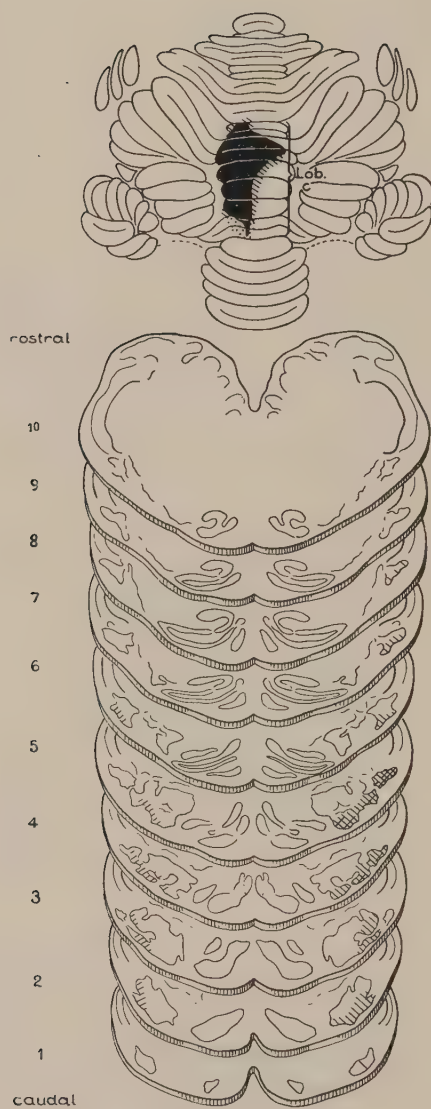


Fig. 6.

Diagram of the findings in rabbit 0.27. Symbols as in Fig. 4.

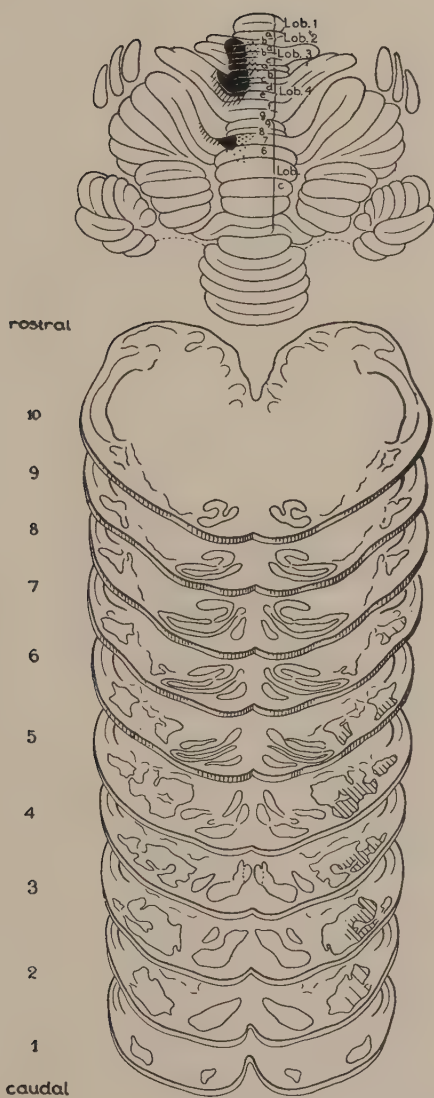


Fig. 7.

Diagram of the findings in rabbit O.128. Symbols as in Fig. 4.

In the *homolateral nucleus reticularis lateralis* changes are found as rabbits O.33 and O.137. Some of the remaining cells are tigrolytic and apparently disintegrating.

This series thus demonstrates that *the lobulus c receives fibers from the nucleus reticularis lateralis*. Furthermore it is seen that the areas showing cellular changes following a lesion of the lobulus c lie within the territory demonstrated in the previous series as the place of origin of the fibers to the entire vermal region. Compared with the findings in the two previous series, the changes in this series, however, are somewhat more restricted spatially and the intensity of the cell-loss is less. Both these facts show that the lobulus c is not the only part of the vermis to receive fibers from the nucleus reticularis lateralis. Further information is given by

Rabbit O.128, 11 days old at operation, killed after 10 days.

(Fig. 7.)

Injury: With the thermo-cauter one side of the anterior lobe has been partially destroyed. The vermal part of the lobulus 3 and partly of the lobulus 4 is injured, as are also accidentally the rostralmost two folia of the lobulus c. Laterally the lesion extends a little farther than the vermis sensu strictiori and partly affects the intermediate part of the lobuli 3 and 4.

In the *homolateral nucleus reticularis lateralis* changes are found as indicated in the diagram in Fig. 7. There is a moderate but distinct loss of cells in the ventro-caudal regions of the nucleus. The limits of this cell-loss are indistinct. Of the remaining cells some are highly tigrolytic, disintegrating, but the majority of them are normal.

From these findings it seems safe to conclude that *the vermis of the anterior lobe receives fibers from the nucleus reticularis lateralis*. The rather insignificant lesion of the lobulus c cannot be responsible for the changes. To what extent the affection of the intermediate part of the anterior lobe contributes to the cell-loss cannot be decided, however. As will be seen the area showing cellular changes following an injury to the medial vermal parts of the anterior lobe falls within that affected after a lesion of the entire vermal region and coincides nearly with that sending fibers to the lobulus c (cf. Figs. 4, 6 and 7).



Fig. 8.

Diagram of the findings in rabbit 0.24. Symbols as in Fig. 4.

Rabbit O.24, 6 days old at operation, killed after 8 days.

(Fig. 8.)

Injury: The lobulus a and the lobulus b have been extirpated by means of a knife. Only a tiny bit of the cortex of the lobulus b is left. The caudal folia of the lobulus c have also been slightly damaged and both fastigial nuclei have been partly removed together with the lobuli a and b.

In the *nuclei reticulares laterales* changes are found as indicated in the diagram of Fig. 8. There is a moderate loss of nerve cells in the hatched areas, and some of the remaining cells are found in retrograde reaction. As will be seen from a comparison of the diagram of the changes in Fig. 8 with the diagram of Fig. 1, showing the cellular types present in the different regions of the nucleus, the changes found in this series are practically restricted to the parvi-cellular portion. As the lesion is bilateral, however, it is difficult to decide exactly whether the remaining parts of the nucleus are completely normal or not. So it cannot be excluded that some very slight changes are present also in the magnocellular portion of the nucleus.

The findings in this series as well as similar results of some other series with injury to the lobulus b (*e.g.* rabbit O.120, lesion of the lobulus b and the nucleus fastigii on one side) indicate that the *lobulus b, the uvula, receives fibers from the nucleus reticularis lateralis, predominantly if not exclusively, from the parvi-cellular portion*. It is not possible to decide if the nodulus, the lobulus a, also receives such fibers, and concerning the nucleus fastigii there is also uncertainty, as it has been impossible to damage these parts of the cerebellum without considerable accompanying injury to the lobulus b, and the diffuse organization of the projection in question prevents drawing conclusions from comparisons between series with only small differences in regard to the lesion. When the quantitative mass of the different parts injured in this experiment are taken into account, however, it appears reasonable that the lesion of the lobulus b is responsible at any rate for a part of the nuclear changes.

So far it has been shown that the vermis of the lobus anterior, the lobulus c and the lobulus b receive fibers from the nucleus reticularis lateralis. Furthermore, it is seen that these fibers take their origin predominantly in the caudal and ventro-lateral parts of the nucleus, *i.e.* primarily the parvi-cellular portion of the

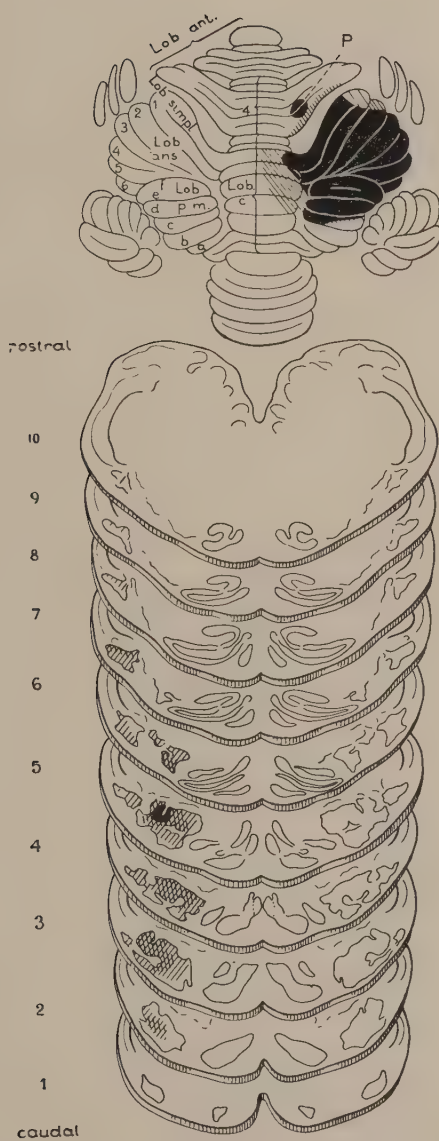


Fig. 9.

Diagram of the findings in rabbit 0.65. Symbols as in Fig. 4.

nucleus. This is especially clear as concerns the lobulus b, the uvula. As the cell-loss in the nucleus is not total even after damage to the entire vermal region (Fig. 4), it can be inferred per exclusionem that also other parts of the cerebellum than the vermal region receive fibers from the nucleus reticularis lateralis. The following series give information concerning this point.

Rabbit O.65, 11 days old at operation, killed after 8 days.
(Fig. 9.)

Injury: Practically the entire lobulus ansiformis and the rostral half of the paramedian lobule on the right side were removed by means of a knife and a pincette. The right half of the lobulus c has also been damaged superficially (see Fig. 9). In the lobulus 4 of the anterior lobe a small "porus" has developed, which however is situated superficially and thus cannot have destroyed fibers to a greater area of the cortex of the anterior lobe.

In the *homolateral nucleus reticularis lateralis* distinct changes are found. There is in some regions a definite loss of nerve cells, accompanied by an increase of the glial cells. Scattered cells are seen with signs of retrograde reaction. The most intense changes are found more dorsally and more rostrally than in rabbit O.33 (Fig. 4) and rabbit O.137 with lesion of the vermis only. Fig. 5 c shows a microphoto of the nucleus in this series at level 3 of the diagram. From a comparison between this picture and Fig. 5 a the more dorsal position of the most massive changes in the present case is obvious.

Although the lobulus c was partly damaged in this series, there can be no doubt that the changes in the nucleus reticularis lateralis are not due to this lesion alone. From a comparison with the findings in the preceding series (rabbit O.33, O.137, O.27) it seems fair to conclude that the cell-loss in the ventro-caudal parts of the nucleus in the present series is a consequence mainly of the lesion of the lobulus c, whereas the major part of the changes, which are located more dorsally and more rostrally, i.e. predominantly within the magno-cellular portion of the nucleus, are due to the lesion of the anso-paramedian lobule. The relatively insignificant lesion in the anterior lobe cannot be responsible for the rather heavy changes. Thus it

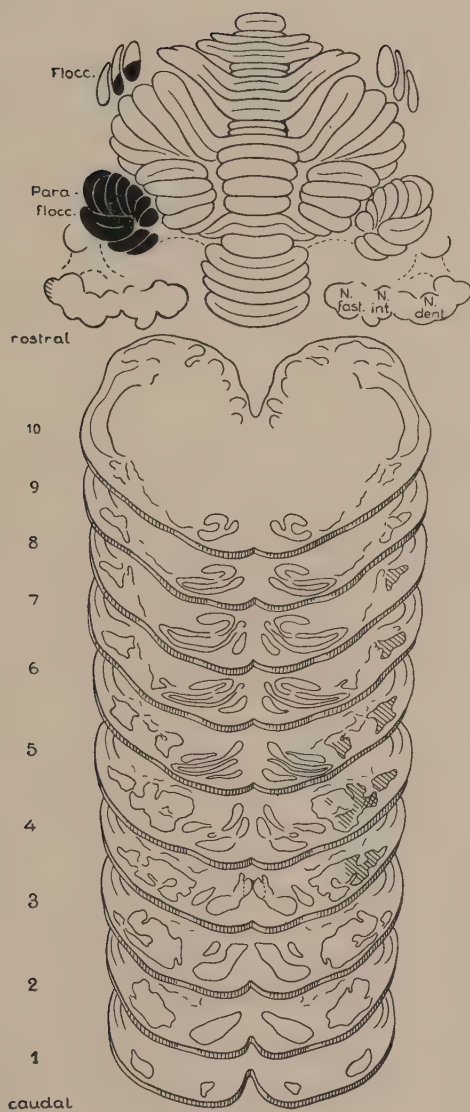


Fig. 10.

Diagram of the findings in rabbit 0.63. Symbols as in Fig. 4.

will be justifiable to state, that *the lobulus anso-paramedianus receives fibers from the nucleus reticularis lateralis, predominantly from its dorsal parts, i.e. the magno-cellular portion.*

That *the lobulus paramedianus participates in this projection* is evident from another series (rabbit O.129, 6 days old at operation, killed after 7 days), where the lesion was confined to the paramedian lobule and only few fibers to the lobulus c were severed. In this experiment (not illustrated) the changes in the nucleus reticularis lateralis were less pronounced than in the preceding experiment, but they were found within the same areas of the nucleus, especially in the lateral part of the magno-cellular portion.

Rabbit O.63, 11 days old at operation, killed after 6 days.

(Fig. 10.)

Injury: The right paraflocculus has been removed after severing its "stalk" with the branches of a little pincette. The cortex is entirely lost, whereas part of the central medullary mass is left intact, and the extreme lateral pole of the nucleus lateralis (dentatus) which extends into the paraflocculus is only slightly damaged. Besides, the flocculus is partly injured, as seen from Fig. 10 because the pincette was pushed a little too far ventrally.

The homolateral nucleus reticularis lateralis shows slight but definite changes in some regions as indicated in Fig. 10, consisting in a moderate loss of cells, and furthermore some of the remaining cells present the pictures typical of the retrograde reaction reproduced in Fig. 3. Most of these cells belong to the medium sized type.

As the lesion of the flocculus in this experiment is relatively insignificant while the paraflocculus is removed entirely, it seems fair to conclude that the changes in the homolateral nucleus reticularis are due mainly if not exclusively to the parafloccular lesion, *i.e. that the paraflocculus receives fibers from the nucleus reticularis lateralis.* As to the flocculus, nothing definite can be said from the findings in the present series. However, some information may be gained from a comparison of this series with others where the lesion comprises the paraflocculus as well as practically the entire flocculus, *e.g.*

Rabbit O.96, 14 days old at operation, killed after 12 days
(not illustrated).

Injury: The paraflocculus is nearly completely destroyed, and likewise the flocculus. The nucleus dentatus is also destroyed in its lateral half.

In the *homolateral nucleus reticularis lateralis* changes are found corresponding to those described in the previous series (rabbit O.63), but besides there is also a considerable loss of cells in the rostral part of the nucleus, (sections 8-9-10 in the diagrams, the subtrigeminal portion), which in the previous series showed only slight changes.

From the findings in this series and others where also the flocculus was damaged and the consequent nuclear changes comprised the rostral part of the nucleus, it *seems probable that the flocculus receives fibers from the nucleus reticularis lateralis, predominantly from the subtrigeminal portion.* The objection might be raised that the difference between the two above-mentioned series is due to the lesion of the dentate nucleus in the latter series. But this appears not to be the case, judging from a comparison with other series, with lesion of the paraflocculus and the flocculus and only slight damage to the lateral-most part of the nucleus dentatus (e.g. rabbit O.116) where the extreme rostral part of the nucleus reticularis lateralis shows rather marked changes.

Owing to the hidden position of the lateral parts of the lobus anterior in the rabbit it is practically impossible to produce lesions of this part of the cerebellum alone. On account of the diffuse nature of the projection from the nucleus reticularis lateralis on the cerebellum it is also difficult to draw definite conclusions from series with lesions of the anterior lobe accompanied by lesions of other parts of the cerebellum as well. However, some hints may be gained from comparisons of this sort. Below a series is presented, which is of interest for the present question.

Rabbit O.99, 16 days old at operation, killed after 11 days.
(Fig. 11.)

Injury: The cortex of the entire lobulus anso-paramedianus has been removed by means of a knife and a pincette, without damage to the para-

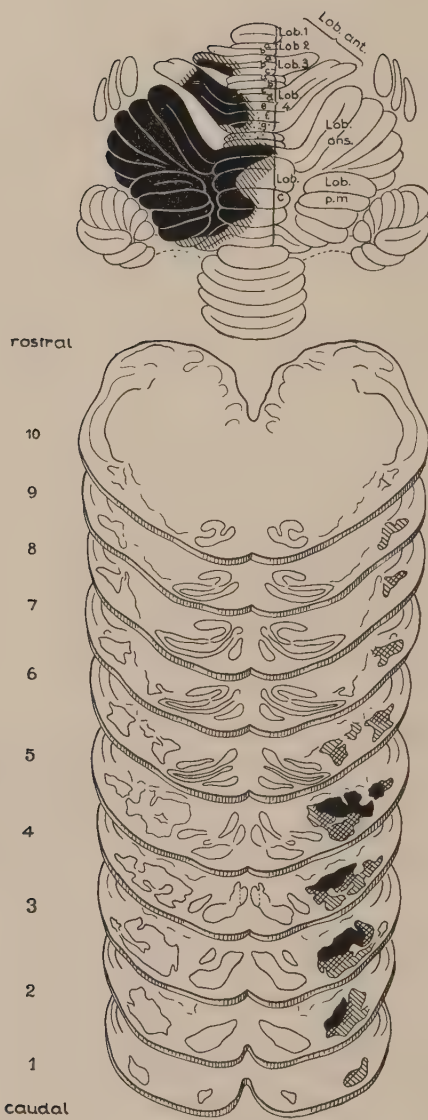


Fig. 11.

Diagram of the findings in rabbit 0.99. Symbols as in Fig. 4.

flocculus or the underlying nuclei, but in addition the lesion also comprises nearly half of the lobulus c and a considerable part of the lobulus 4 and partly the lobulus 3 of the anterior lobe, leaving however intact the extreme lateral part as well as the median part of the vermis.

In the *homolateral nucleus reticularis lateralis* extensive and rather heavy changes are found, as appears from the diagram in Fig. 11. In the parts of the nucleus most severely affected (black in the diagram) more than half of the cells have disappeared, and of the remaining cells a good many are disintegrating, extremely tigrolytic and with indistinct contours, whereas others present the picture of the retrograde reaction. There is some increase in the glia. As will be seen, changes of lesser intensity are found throughout the entire nucleus.

From the findings in the preceding series it can be concluded that the major part of the changes found in the parvicellular portion of the nucleus in the last series are due to the injury to the divisions of the vermis included in the lesion. As the changes in the magno-cellular portion are far more intense in this series than in rabbit O.65 (Fig. 9) where practically the entire ansoparamedian lobule was removed, it seems fair to conclude that the accompanying lesion of the "hemispherical parts" of the anterior lobe is the cause of part of the changes in this portion of the nucleus, especially to the changes in its dorsomedial areas at levels 2-4 in the diagram, *i.e.* that the "*hemispherical part*" of the anterior lobe receives fibers from the *nucleus reticularis lateralis*, especially from the dorso-medial parts of the magnocellular portion. It might be objected that the more intense changes in the last series are an expression only of the sum of changes following lesions of the ansoparamedian lobule and the injured areas of the vermis. Of course the diffuse projection of the nucleus will contribute rather heavily to intensify and make more extensive the ensuing nuclear changes where more parts of the cerebellum are injured, more so the more extensive the cerebellar lesion. However, that this factor alone cannot be responsible in the last mentioned series is indicated partly by the severity of the changes, but primarily by the fact that the most intense changes in this series are found also in regions of the nucleus which showed

only slight or no detectable changes in other series with lesions of either the vermal region or the anso-paramedian lobule.

Summary of the results in rabbits.

Above it has been shown by direct evidence that in the rabbit several of the cerebellar lobules receive fibers from the homolateral nucleus reticularis lateralis, viz. the lobuli b, c, the vermis of the anterior lobe, the ansiform and the paramedian lobules and the paraflocculus, and indirectly the conclusion was reached that the flocculus and the lateral parts of the anterior lobe likewise receive such fibers. As concerns the lobulus a, the nodulus, no unequivocal evidence can be brought forward. A priori it appears probable that this lobule, like the flocculus, has connections with the nucleus as these two parts of the cerebellum, forming together the flocculo-nodular lobe of *Larsell*, in regard to their other known fiber connections behave in exactly the same manner [efferent and afferent connections predominantly with the vestibular nuclei (*Ingvar* 1918, *Dow* 1936, 1938) and, besides, receiving fibers from the same part of the medial accessory olive (*Brodal* 1940 c)]. Thus as far as can be judged from the experiments it appears *probable that all parts of the cerebellar cortex receive fibers from the nucleus reticularis lateralis*. Of the different parts, *the vermal region receives considerably more than half of the total fiber mass*. Concerning the cerebellar nuclei nothing definite can be said.

From a perusal of the experiments described above and others not referred, it is furthermore evident that the different parts of the cerebellum indeed are connected predominantly with certain regions of the nucleus, but that *the projections areas of the different parts overlap to a considerable extent*, so that *actually none of the lobules dominates its nuclear territory alone*. In spite of this it can be said that *the parvi-cellular portion of the nucleus sends its fibers predominantly to the vermis, the magno-cellular portion predominantly to the lobulus anso-paramedianus, the paraflocculus and the "hemispherical parts" of the anterior lobe and the subtrigeminal portion mainly to*

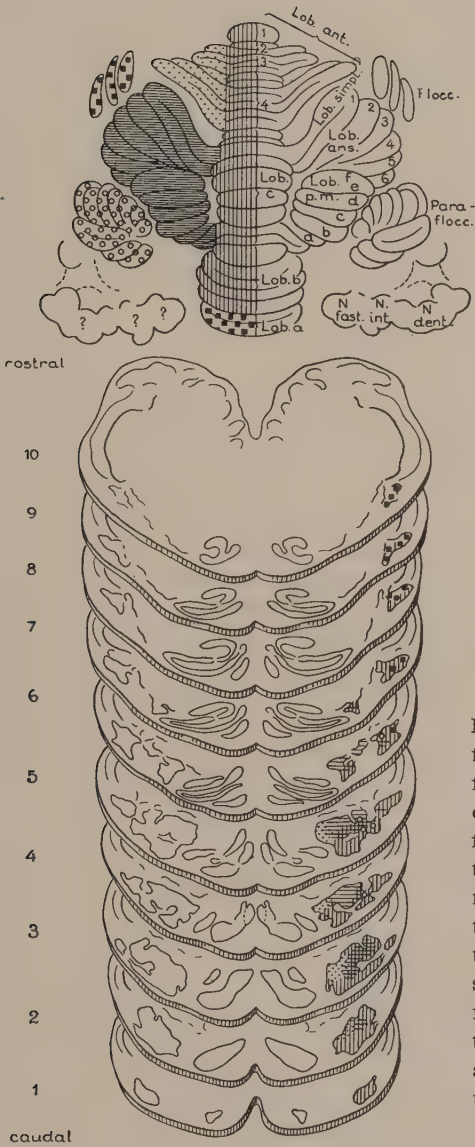


Fig. 12.

Diagram summarizing the findings in the rabbit. Different parts of the cerebellar cortex are labelled with different symbols. The areas of the nucleus reticularis lateralis marked as the respective corresponding parts of the cerebellum are only those sending the majority of their fibers to that part. The extensive overlapping which actually exists in the projection is not shown in the diagram. (Cf. the text.)

the flocculus and probably the nodulus, the flocculo-nodular lobe.

On account of the diffuse localization the presentation of a diagram of the entire projection, which appears desirable, can be made according to one of two principles: Either the entire territory of the nucleus reticularis lateralis belonging to each of the cerebellar lobules can be indicated by its distinct symbols, which however will give a diagram burdened with details and difficult to interpret, or only the area which sends the major part of its fibers to the separate lobules is marked with the corresponding symbols.

In the latter case a diagram results which will necessarily be rather schematic, but which has the advantage of being easier to survey. The diagram presented in Fig. 12, summarizing the findings of the experiments, is made according to the latter principle. As will be seen only five separate divisions of the cerebellar cortex are dealt with in the diagram, namely: the entire vermis (except the lobulus a), the lobulus anso-paramedianus, the extra-vermian parts of the anterior lobe, the para-flocculus and the flocculo-nodular lobe (consisting of the flocculus and the lobulus a). When reading the diagram, therefore, it has to be kept in mind that the projection is far less localized than appears from the diagram, and for more exact information the descriptions of the separate series should be consulted. The question-marks in the cerebellar nuclei indicate that it has not been possible to ascertain whether these parts of the cerebellum also receive fibers from the nucleus reticularis lateralis.

B. Cats.

The findings in the cat correspond very well with those in the rabbit. On this account only a few series will be illustrated.

Cat O.80, 20 days old at operation, killed after 11 days.

(Fig. 13.)

Injury: With a tiny knife a paramedian incision was made in the cerebellum on the border between the vermis and the right hemisphere

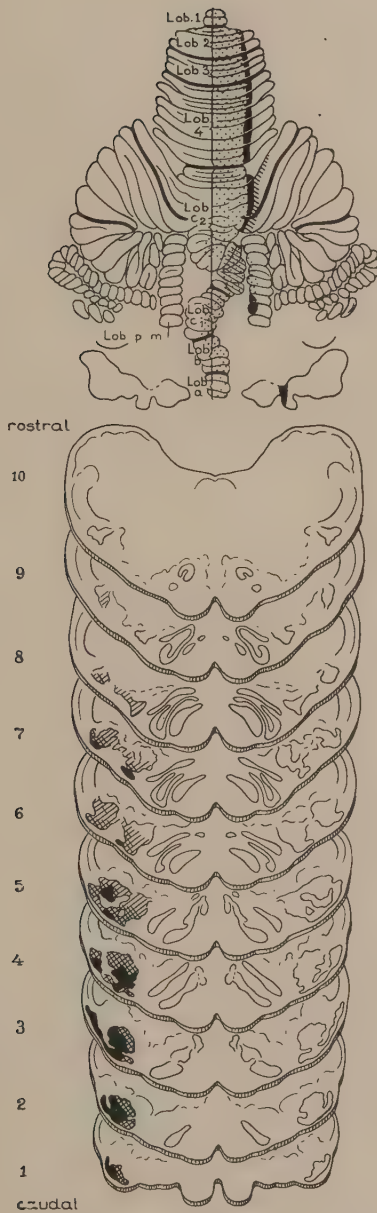


Fig. 13.

Diagram of the findings in cat O.80. Symbols as in Fig. 4.

as indicated in Fig. 13. Microscopically it is seen that the lesion is sharply delimited as planned, accompanied only by slight superficial damage to some folia of the ansiform lobule and a lesion of a couple of folia of the paramedian lobule. The lesion extends to the ventricular surface of the cerebellum, penetrating the medial part of the nucleus interpositus. Only most caudally, lateral to the lobulus a, the lesion does not quite reach the ventricular surface. On this account it is probable that some of the fibers to this lobule and likewise some fibers to the lobulus b, have not been severed, whereas the fibers to the entire rest of the vermis must have been cut. In the lobulus c, a small "porus" (*Spatz*) has developed and has probably also affected some fibers to the left half of the lobule.

In the *right nucleus reticularis lateralis* marked changes are found as indicated in the diagram in Fig. 13. There is a massive loss of nerve cells, though of different intensity in the different parts of the nucleus. All told, approximately only $\frac{1}{3}$ or somewhat less of the total mass of cells is left. Most of the remaining cells are normal, only scattered individuals are found to show signs of retrograde changes. There is a considerable increase in the glia.

The findings in this experiment correspond very well with those made in the rabbit after a similar injury (cf. Fig. 4, rabbit O.33). Thus it is evident that also in the cat *the vermal region receives fibers from the nucleus reticularis lateralis, predominantly from its parvi-cellular portion*. It is furthermore obvious that *this part of the cerebellum receives more of the fibers from the nucleus than the lateral parts* (hemispheres, flocculus and paraflocculus) a fact which is also shown by series with lesions of the hemispheres (cf. below). When the relative mass of the vermis and the hemisphere is taken into consideration, *it appears that the vermal region is far more richly supplied with fibers from the nucleus reticularis lateralis than the hemisphere*.

From other series information can be gained as to which parts of the vermis are the end stations of these fibers. The findings correspond well with those made in the rabbit and may on this account be dealt with more briefly.

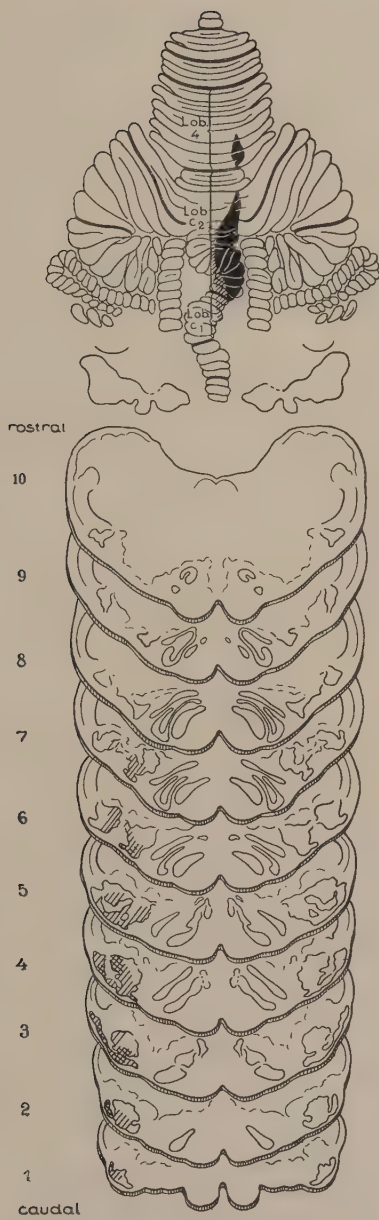


Fig. 14.

Diagram of the findings in cat 0.41. Symbols as in Fig. 4.

Cat O.41, 13 days old at operation, killed after 11 days.

(Fig. 14.)

Injury: The lobulus c_2 is practically totally destroyed on the right side, on the left side the damage to the same lobulus is only partial and superficial. Besides, the lesion extends a little into the anterior lobe (lobulus 4), and probably some fibers to the lobulus c_1 have been cut.

In the *nuclei reticulares laterales* no convincing changes can be found in the left, whereas in the right nucleus there is a moderate loss of cells in some parts of the nucleus (v. Fig. 14). Of the remaining cells some present the picture of retrograde reaction.

The findings in this experiment supplement the results obtained in rabbits and are of special interest as they demonstrate that the lobulus c_2 , the youngest part of the "vermis", belonging to the "neo-cerebellum", receives fibers from the *nucleus reticularis lateralis*. In the rabbit a lobulus c_2 cannot be clearly identified, the entire lobulus c apparently forming an entity.

From other series it can be seen that the lobulus b as in the rabbit also participates in the projection on the nucleus *reticularis lateralis*, e.g.,

Cat O.53, 3 weeks old at operation, killed after 11 days
(not illustrated).

In this animal the lobulus b was destroyed practically entirely and likewise the lobulus a. The lobulus c_1 was also partly damaged, and the left nucleus fastigii was moderately injured at its ventral margin. In both *nuclei reticulares laterales* there is found a considerable loss of cells within the territories affected in cat O.80 (v. Fig. 13), but the changes are of a lesser intensity and are spatially more restricted, affecting mainly the parvi-cellular portion, especially in the caudal part, sections 1-3.

It must be permissible to infer from these findings that the lobulus b receives fibers from the *nucleus reticularis lateralis*, predominantly from its parvi-cellular portion. Probably the same holds good also for the lobulus a, the *nodulus*, although this cannot be definitely proved, as the lobulus a was not damaged alone in any series. As was the case in the rabbit it must likewise be left an open question, whether the lesion of the nuc-

leus fastigii contributes to the cellular changes in the nucleus reticularis lateralis.

From a comparison between this series and the preceding, cat O.41, an assumption of some interest may be made. Following a lesion of the lobulus b (and a, and partly of the lobulus c_1 , cat O.53) the most intense changes are found in the caudal part of the parvi-cellular portion of the nucleus reticularis lateralis, whereas the magno-cellular portion is but slightly affected and only in its ventral and caudal parts. When, however, the lobulus c_2 is damaged as in cat O.41 (Fig. 14), the ensuing nuclear changes are of a lesser intensity in the parvi-cellular portion especially in the caudal sections (levels 1-2 in the diagram), but the affection of the magno-cellular portion is more pronounced. It is tempting to regard this difference as an expression of the different age and functional importance of the two lobules in question, pointing towards the intimate relationship between the lobulus c_2 and the anso-paramedian lobule (cf. lobus medius of *Ingvar*), as the anso-paramedian lobule receives fibers predominantly from the magno-cellular portion of the nucleus (cf. below).

Unfortunately the vermis of the anterior lobe was not damaged in any series without considerable accompanying injury to other parts, so the projection of this part of the cerebellum cannot be directly demonstrated. Granting an analogy with the conditions in the rabbit, however, it may be assumed that also in the cat the *vermis of the anterior lobe receives fibers from the nucleus reticularis lateralis*, an assumption which is substantiated by a comparison between different series with lesions of this part of the cerebellum together with other lobules. For instance, the pronounced changes following the section of the fibers to the entire vermal region (cat. O.80, Fig. 13) cannot be entirely accounted for by adding the changes following a lesion of the lobulus c_2 (cat O.41, Fig. 14) to those following an extensive lesion of the lobulus b and partly lobulus a and c_1 . Accordingly the projection of this part is represented in the diagram summarizing the results of the investigation (Fig. 18).

The conclusion drawn from the experiment on cat O.80 (Fig.

13), that the "hemispherical" parts of the cerebellum also receive fibers from the nucleus reticularis lateralis, is substantiated by the findings in several series, *e.g.*, the following.

Cat O.69, 3 weeks old at operation, killed after 11 days.

(Fig. 15.)

Injury: The entire anso-paramedian lobule has been extirpated, and the caudal part of the paraflocculus has also been removed, especially the caudal part of the dorsal crus. Furthermore the flocculus is partly damaged, as a considerable part of the fibers entering it have been severed. Finally there is a small lesion in the anterior lobe and the lateral part of the nucleus dentatus as seen from the figure, and as a consequence of a fissure which has developed dorsally to the dentate nucleus a few fibers to the lobuli b and c have been cut.

Throughout the entire homolateral nucleus reticularis changes are found, which in some regions are rather massive, in others only slight as indicated in the diagram in Fig. 15. There is some cell-loss, and of the remaining cells some are highly tigrolytic, apparently disintegrating, whereas a considerable portion exhibit the picture of acute retrograde changes.

As will be seen from the diagram, the extirpation of the entire lobulus anso-paramedianus with parts of the paraflocculus and flocculus is followed by rather intense changes in the nucleus reticularis lateralis. Furthermore, from a comparison between the findings in this series and those in cat O.80 (Fig. 13) it is a striking fact that the most intense changes occupy different parts of the nucleus in the two instances, although in both cases practically no part of the nucleus is quite normal. Obviously the vermal region is the main end-station for the fibers from the parvi-cellular portion of the nucleus, the magno-cellular portion for the fibers from the "hemispheres". However, from the series presented so far no information is gained as to the question of which parts of the "hemispheres" are the end-stations for these fibers, a question of considerable interest. Other series elucidate this point, some of which will be recorded below.

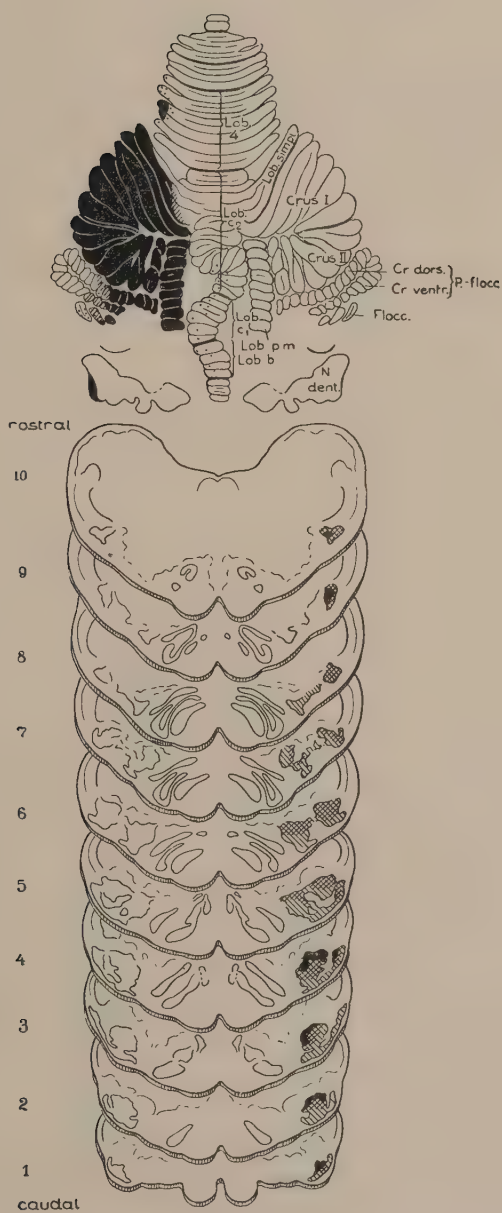


Fig. 15.

Diagram of the findings in cat O.69. Symbols as in Fig. 4.

Cat O.32, 10 days old at operation, killed after 11 days.

(Fig. 16.)

Injury: With a tiny knife and a pincette the rostral two-thirds of the right lobulus paramedianus were removed with only superficial injury to the neighbouring folia of other lobules as indicated in Fig. 16.

In the *homolateral nucleus reticularis lateralis* rather slight but nevertheless distinct changes are found. The areas marked with hatchings in Fig. 16 show a distinct loss of cells. Most of the remaining cells are quite normal, but between them several cells are seen showing distinct tigrolysis and loss of contours. There is also some glial increase in these parts of the nucleus.

This series thus demonstrates conclusively that *the paramedian lobule in the cat receives fibers from the nucleus reticularis lateralis*. Furthermore it appears that these fibers take their origin *predominantly from the magno-cellular portion*, especially from its dorso-lateral parts.

That the ansiform lobule likewise has connections with the nucleus reticularis lateralis is shown by several series, *e.g.*,

Cat O.76, 3 weeks old at operation, killed after 13 days
(not illustrated).

Injury: The right ansiform lobule is partly damaged, as the crus I is nearly totally extirpated and some of the fibers from the crus II are severed. Apart from this, no parts of the cerebellum are injured.

In the *homolateral nucleus reticularis lateralis* a slight loss of cells is found in the magno-cellular portion, especially in its dorsolateral parts.

Cat O.74, 3 weeks old at operation, killed after 10 days
(not illustrated).

Injury: Somewhat more than the rostral half of the crus I of the ansiform lobule has been extirpated, with only superficial damage to some of the neighbouring folia of the paraflocculus and the extreme lateral part of the lobus anterior.

In the *homolateral nucleus reticularis lateralis* slight changes are found in the same regions as in the previous series.

From these series the conclusion can be drawn that *the ansiform lobule receives fibers from the nucleus reticularis lateralis*,

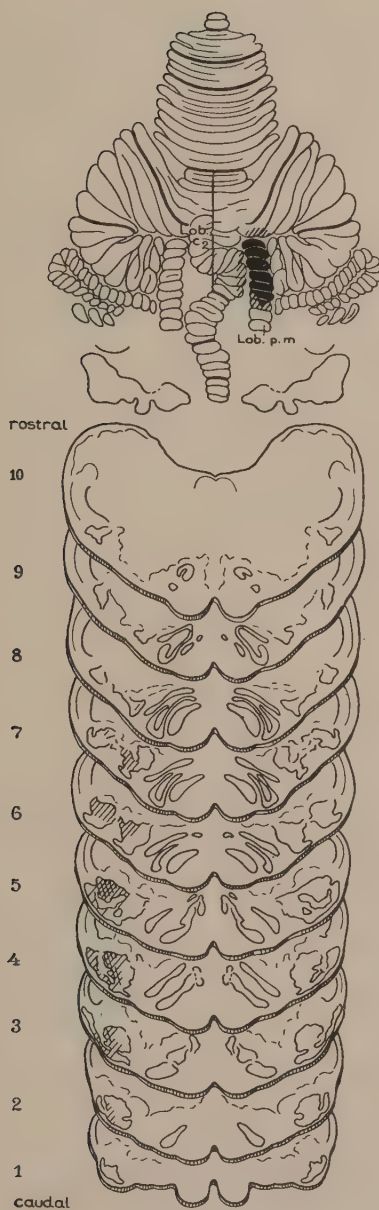


Fig. 16.

Diagram of the findings in cat O.32. Symbols as in Fig. 4.

predominantly if not exclusively from the magnocellular portion. The degree and distribution of changes following lesions of the ansiform and paramedian lobules are rather slight, a finding which is in harmony with the previously mentioned fact, that the vermal region is far more richly provided with fibers from the nucleus reticularis lateralis than are the "hemispheres".

As can be seen from Figure 15, the changes in cat O.69, where the entire anso-paramedian lobule was extirpated, are rather intense and widespread, and can scarcely be accounted for by the lesion of this lobule alone. And even if allowance is made for the accompanying section of some fibers to the vermis, the cell loss is remarkably large. Especially striking is the distinct loss of cells in the subtrigeminal portion, as it was not found to this degree in any of the previously recorded series. This affection of the subtrigeminal portion might be due to the accompanying lesion of the flocculus or the paraflocculus in the series (cat O.69), as both these parts of the cerebellum were intact in the previously treated series. Information concerning this point is given by

Cat O.75, 3 weeks old at operation, killed after 14 days
(not illustrated).

Injury: The right paraflocculus has been partly extirpated. Somewhat more than the rostral half of the paraflocculus is lacking. Besides, there is superficial damage to one folium of the flocculus, which however affects only the cortex in a circumscribed area without damage to the underlying white matter, and thus probably is negligible in this connection. In the *homolateral nucleus reticularis lateralis* a slight loss of cells is found in the magno-cellular portion, most prominent at levels 4-6 of the diagram. Some of the remaining cells are t!grolytic. In the subtrigeminal portion of the nucleus no changes can be detected.

From the findings in this series the conclusion must be drawn that *the paraflocculus participates in the cerebellar projection of the nucleus reticularis lateralis* and that *its fibers originate from the magno-cellular portion.* Furthermore a comparison between the findings in this series and those preceding (cat O.69, Fig. 15, cat O.32, Fig. 16 and cat O.76 and O.74) leads to the

conclusion that the rather intense changes in the subtrigeminal portion of the nucleus in cat O.69 must be due to the accompanying lesion of the flocculus in that experiment, *i.e.* that *the flocculus receives fibers from the nucleus reticularis lateralis, predominantly from its subtrigeminal portion*. A confirmation of this conception is supplied by the fact that also in other series this part of the nucleus is unchanged when the ansiform lobule, or parts of it, or the paraflocculus are damaged and only slightly affected with lesions of the vermis even if the fibers to the entire vermal region are severed as in cat O.80 (Fig. 13).

As was the case in the rabbit, in no experiment has the lesion been confined to the nodulus, the lobulus a. On account of the intimate relationship between this lobule and the flocculus it appears *probable that also the lobulus a receives fibers from the nucleus reticularis lateralis and especially from the subtrigeminal portion as the flocculus*. The slight changes which have been observed in this part of the nucleus in series with lesions of the vermis where the lobulus a has been included in the lesion may be interpreted as a confirmation of this conception.

Cat O.62, 25 days old at operation, killed after 1½ days.

(Fig. 17.)

Injury: The lateral parts of the lobuli 3 and 4 of the anterior lobe have been practically totally destroyed and the lesion extends a little into the vermal region (the border between the vermis and lateral parts of the anterior lobe is chosen as a rostral continuation of the border between the paramedian lobule and the vermis). As the lesion farther caudally penetrates as a slit approximately on the border between the ansiform lobule and the vermal region, ventrally reaching close to the nucleus interpositus, the fibers to the lobuli c_2 and c_1 and, to a lesser degree, also to the lobuli b and a have been cut. The medial parts of the crus I and the lobulus simplex are also damaged in a circumscribed area (see Fig. 17).

In the *homolateral nucleus reticularis lateralis* marked changes are found in the caudal half. In the areas indicated by black in the diagram in Fig. 17 the majority of the cells have disappeared. Only a few normal individuals are left, besides some which are highly tigrolytic and apparently disintegrating. Cell-loss of a lesser intensity is furthermore

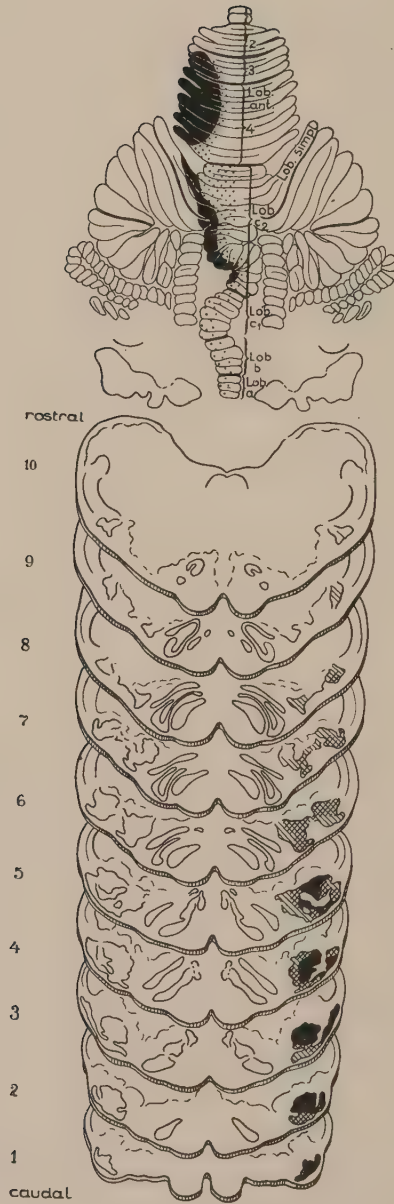


Fig. 17.

Diagram of the findings in cat 0.62. Symbols as in Fig. 4.

found nearly throughout the entire nucleus, accompanied by a marked increase in the glial elements.

This series differs from the others presented above in the extensive lesion of the lateral parts of the anterior lobe. From the findings in cat O.80 and others with partial lesions of the vermis the cell-loss following lesions of the vermal region is known. Comparing now the changes in such series with those in the present, it is striking that the changes in the last experiment, besides comprising the areas previously determined as the projection areas of the vermis, are more extensive, as they occupy also the larger part of the magno-cellular portion of the nucleus at levels 2-4 of the diagram. Furthermore the changes in the last series in this part of the nucleus are more intense, as nearly all cells have disappeared. As the ansiform lobule receives only a minor part of the fibers from the ventro-lateral regions of the magno-cellular portion of the nucleus at these levels (see cat O.69, Fig. 15) it must be justifiable to conclude that the "*hemispherical part*" of the anterior lobe in the cat receives fibers from the magno-cellular portion of the nucleus *reticularis lateralis*, especially at levels 2-4 of the diagram.

As was the case in the rabbit, and for the same reasons, no information concerning the eventual connections of the cerebellar nuclei with the nucleus *reticularis lateralis* can be obtained.

Summary of the results in cats.

The findings in the experiments on cats are in good accordance with those obtained in rabbits, and may be summarized thus: *Practically all cells of the nucleus reticularis lateralis send their fibers to the homolateral half of the cerebellum, where they are distributed to all parts of the cortex* (only concerning the lobulus a, the nodulus, can some doubt remain) and *the vermis receives more than half of the total mass of fibers*. Although this projection is rather diffusely organized, a *certain degree of localization is nevertheless present*. This is presented schematically in Fig. 18, elaborated after the same principle as

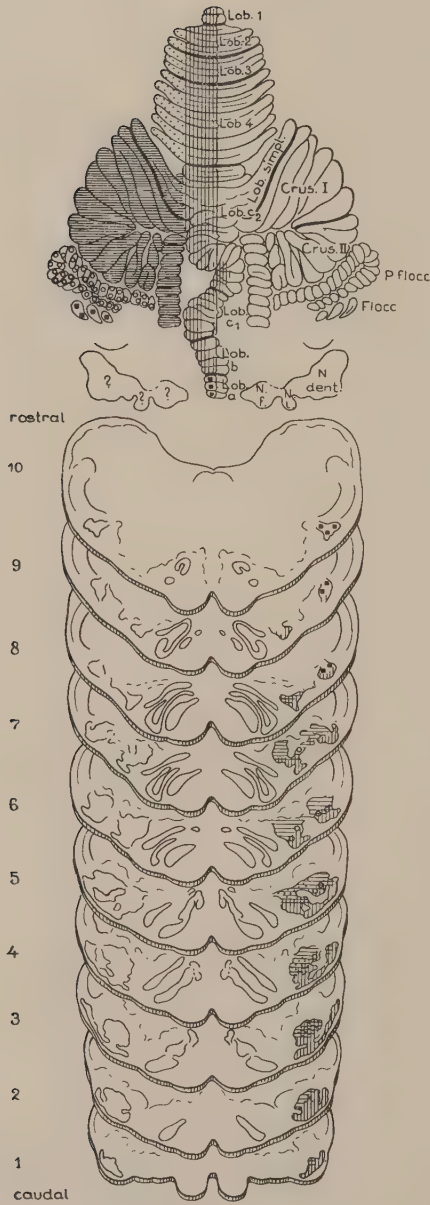


Fig. 18.

Diagram summarizing schematically the findings in the cat after the same principle as for the rabbit in Fig. 12. (Cf. the text.)

the diagram for the rabbits (Fig. 12). *The parvi-cellular portion of the nucleus sends its fibers predominantly to the vermis (the lobulus a probably excepted), the magno-cellular portion predominantly to the lobulus anso-paramedianus, the paraflocculus and the "hemispherical parts" of the anterior lobe; and the subtrigeminal portion sends its fibers predominantly to the flocculus and probably the nodulus (lobulus a), the flocculo-nodular lobe.* Whether the cerebellar nuclei receive fibers from the nucleus reticularis lateralis cannot be decided from the present material, a circumstance indicated in the diagram by the question-marks in the nuclei.

It should again be emphasized, that the projection areas of the different cerebellar subdivisions are by no means so sharply delimited as appears from the rather schematically constructed diagram. In reality no part of the nucleus sends its fibers to only one minor part of the cerebellum, the degree of overlapping being rather extensive, as can be seen from a comparison between the different series illustrated above.

DISCUSSION

As far as can be judged from the available literature¹ the cerebellar connections of the nucleus reticularis lateralis have not previously been the object of successful detailed experimental investigations. As has been mentioned in the introduction, only studies on the effects of section of the restiform body or of extirpation of the cerebellum are to be found. Apart from this, some authors have published conclusions reached on the basis of findings in cases of cerebellar malformation or cerebellar atrophy, of which the conceptions of *Brun*, *Marburg* and *Ziehen* were mentioned in the introduction. Before discussing the results obtained in this investigation from a general point of view, some data from the literature will be dealt with.

The assumptions of *Marburg* (1924) that the "lobi laterales"

¹ On account of the present war, a considerable part of the foreign literature from 1940 and later has not been accessible.

and of *Ziehen* (1934) that the vermis receives fibers from the nucleus reticularis lateralis conform with the results of the present investigation. Concerning the conclusions reached by *Brun* (1917-18, 1925) however, the results are not in agreement, as *Brun* (1925) is inclined to assume a projection of the lateral magno-cellular portion of the nucleus on the flocculus, whereas the experiments presented in this paper indicate that the subtrigeminal portion is in connection predominantly with the flocculus. From a study of the descriptions and figures of the two cases of cerebellar malformation published by *Brun* (1917-18, aplasia and hypoplasia neo-cerebellaris) however, no support for his opinion can reasonably be drawn. The only part of the cerebellum which was practically normal was the flocculus in both cases, whereas the vermis was partially hypoplastic, respectively practically normal (case 2) and the hemispheres were markedly reduced and aplastic, respectively hypo-plastic. Of the nucleus reticularis lateralis *Brun* says that the magno-cellular lateral "Hauptkern" was entirely wanting (respectively "hochgradig reduziert"), in the medial parolivary portion only scattered nerve-cells could be found and the "Quintusportion" was well developed. If any conclusion concerning the interrelationship between the nucleus and the cerebellum should be drawn from these findings it must reasonably be that the flocculus is probably related to the subtrigeminal portion (Quintusportion), a result in agreement with the experimental findings presented here, provided that his "Quintusportion" corresponds to the part of the nucleus in the rabbit and the cat designated in this paper as the subtrigeminal portion. Furthermore the fact that the maximal changes in the nucleus reticularis lateralis in both cases were found in the magno-cellular lateral "Hauptportion" might be taken as an indication of a relationship between this part of the nucleus and the "hemisphere", a conclusion which is probably in conformity with the experimental results. The above-mentioned statement of *Brun* apparently refers to one of his cases of cerebellar malformation (1925, p. 196) which was later described in greater details by *Mackiewicz* (1935). In this case only a rudiment of the left hemisphere and the left part of the

vermis was found and the flocculus was also greatly reduced but somewhat less affected than the rest. In the nucleus reticularis only some cells were found in the lateral magno-cellular "Hauptportion". Nor does this case convince the reader of the existense of a connection between the flocculus and the magno-cellular portion of the nucleus in man.

A perusal of some of the numerous other papers dealing with cerebellar malformation and cerebellar atrophy in order to obtain information concerning the relationship between the nucleus reticularis lateralis and the different parts of the cerebellum, yields evidence which is very conflicting. In some cases of cerebellar malformations the nucleus is described as normal, in spite of the presence of marked changes in the cerebellum (e.g. *Lyssenkow* 1931) or no definite changes could be detected (e.g. *Strong* 1915), in others the nucleus was changed, but often no detailed description is given. A case published by *Krause* (1929) deserves special consideration as his findings are in good accord with the experimental results. In *Krause's* case the malformation comprised mainly the hemispheres and the lobulus medius medianus of *Ingwar* (lobulus c_2), whereas the flocculus, paraflocculus and the rest of the vermis were more normal. Of the portions of the nucleus reticularis lateralis the "Quintusportion" was rather well developed, the "parolivare Portion" likewise, but the cells were reduced in number and smaller than normal, and the magno-cellular lateral "Hauptportion" showed a considerable reduction of the cells. These data might indicate that the flocculus receives fibers from the subtrigeminal portion, the hemispheres and the lobulus medius medianus (lob. c_2) from the lateral magno-cellular portion, and the rest of the vermis from the "parolivar" portion.

The findings in cases of cerebellar atrophies are likewise very conflicting. In some cases the nucleus reticularis lateralis was found without changes, (e.g. *Preisig* 1912, *Brouwer* 1913). In others the nucleus was practically free from nerve cells (e.g., *Winkler* 1924), in still others only parts of the nucleus were affected. *Bakker* (1924), for instance, describes a case classified as olivo-ponto-cerebellar atrophy where the atrophy was some-

what less pronounced in the vermis and flocculi than in the hemispheres. In this case cells were left in the subtrigeminal portion of the nucleus reticularis lateralis.

The divergent findings in cases of cerebellar malformations and cerebellar atrophies necessarily lead to the conclusion that material of this kind is very little or not at all suitable for study of the cerebellar connections.¹ When the findings as shown above in some cases are in accord with the experimental results, this can be noted as a corroboration, without however over-emphasizing its importance. Another circumstance also makes a comparison between the experimental findings and those obtained from study of pathological material difficult, namely the fragmentary knowledge of the comparative anatomy of the nucleus reticularis lateralis. From the available literature it seems probable that the extreme rostral part of the nucleus, lying in the rabbit and the cat closely ventral to the nucleus tractus spinalis n. V., corresponds to the nucleus subtrigeminalis or Quintus-Anteil in man as assumed in the previous discussion. Furthermore the magno-cellular portion is probably homologous at least to part of the magno-cellular portion of the nucleus in man (Hauptportion). But which part of the nucleus in man corresponds to the parvi-cellular portion in the rabbit, cat and monkey, is yet an open question.

From the preceding discussion thus only the meagre conclusion can be drawn, that *certain data obtained from a study of human cases make it probable that the conditions in man are principally similar to those existing in the experimental animals.*

From the point of view of cerebellar localization and cerebellar function the results of the present experiments are of considerable interest. The demonstration that the fibers from the nucleus reticularis lateralis are distributed to the entire cerebellar cortex (and the cerebellar nuclei?) and not only to certain divisions of the vermis (especially the lobus anterior and the pyramis) does not fit well into our present conception of the

¹ In my paper on the olivo-cerebellar localization (1940c) the reasons for this are discussed more broadly (pp. 125-129).

cerebellum and its functional localization. As was mentioned in the introduction, apparently it is the prevailing view that the main afferent impulses to the nucleus reticularis lateralis are derived from the ascending fibers in the antero-lateral column of the spinal cord, besides perhaps from some fibers from the posterior funiculus. Then it might be expected that the efferent fibers from the nucleus would behave like the spino-cerebellar fibers and terminate only in the above-mentioned parts of the vermis, as has turned out to be the case (*Brodal* 1941) with another fiber system, namely: the fibers from the nucleus cuneatus externus (nucleus *Monakow*), which in regard to their cerebellar terminations correspond closely to the spino-cerebellar systems, as might be expected since the afferent fibers to this nucleus are fibers of the funiculus cuneatus derived from the cervical and upper 4-5 thoracic posterior roots (*Ferraro and Barrera* 1935 et al.). The distribution of the efferent fibers from the nucleus reticularis lateralis to the entire cerebellar cortex thus apparently brings confusion into the current conception of the cerebellum and its functional subdivision.

However, a closer examination of the data on which the conception is based, that the afferents to the nucleus are ascending fibers from the antero-lateral column, makes it somewhat doubtful whether these may be the only or even the principal afferent paths to the nucleus. In the experimental studies on division of the antero-lateral column or lesions of the spino-cerebellar tracts which have been published, a massive tract has never been traced to the nucleus reticularis lateralis, always only scattered fibers have been seen to enter it. And *Cajal* (1909) describes numerous collaterals to the nucleus from the ascending fibers, but not terminals. From these data it appears improbable that the ascending fibers to the nucleus reticularis lateralis constitute its main afferent path. (The possibility even exists that the degenerated fibres traced to the nucleus in Marchi-preparations are only collaterals, as mentioned by *Blakeslee, Freiman and Barrera*). If this be so, the cerebellar terminations of the efferent fibers of the nucleus are no longer a source of confusion in the conception of the cerebellum. But, on

the other hand, a new problem arises: the main afferent fibers to the nucleus reticularis lateralis must be sought for elsewhere. As cerebellofugal fibers to the nucleus can be left out of the question, only descending fibers from higher levels of the brain remain as a source for the principal afferent impulses. If the main afferent fibers to the nucleus reticularis lateralis are of this type, the nucleus might appropriately be classed together with the inferior olive and the pontine nuclei, as a relay station between the cortex cerebri-striate body and the cerebellum, as suggested, for instance, by *Kappers, Huber and Crosby*.

Unfortunately, however, in the literature only sparse data concerning this question can be found. *Cajal* (1909) describes collaterals from the rubro-spinal tract entering the nucleus reticularis lateralis; but in studies of experimental lesions of the red nucleus, fibers of this kind are not mentioned (e.g. *Verhaart* 1936); nor are fibers from the brachium conjunctivum descendens described as ending in the nucleus (*Allen* 1924 *et al.*). Assuming an analogy with the olivo-cerebellar projection (both systems being distributed to the entire cerebellar cortex), the substantia reticularis medullae oblongatae, pontis et mesencephali might be thought of as a source of such descending fibers. But, e.g., *Papez* (1926) does not describe fibers of this course in his numerous experiments with lesions of the reticular substance; nor are they mentioned by *Weisschedel* (1938) in his studies on normal human material or by *Papez* and *Stotler* (1940) in their description of normal and pathological human cases.

In spite of these negative findings, the possibility that the nucleus reticularis lateralis, besides ascending fibers, also receives fibers from more rostral parts of the brain stem can scarcely be strictly denied. In general, negative results of this kind ought not to be over-emphasized, especially in instances such as the present, as the nucleus reticularis lateralis obviously has not attracted the interest of the authors in any considerable degree; and the possibility must be admitted, that fibers of this kind may have been overlooked on this account. Future research will have to decide whether the nucleus reticularis lateralis re-

ally receives all or most of its fibers from parts of the brain stem placed more rostrally, thus solving the puzzle of the omni-cerebellar termination of the fibers from the nucleus reticularis lateralis, or whether the current conception of the subdivision and functional localization in the cerebellum has to be changed. Besides experimental studies also comparative-anatomical investigations of the nucleus may possibly give valuable hints concerning this problem, and will undoubtedly till a gap in our knowledge.

As previously mentioned the data found in the literature concerning the anatomy of the nucleus reticularis lateralis in different animals are very scanty. On this account a discussion of the results of this experimental investigation from a comparative-anatomical point of view, which might have been desirable, cannot be made. However, another question of general neuro-anatomical interest is raised by the findings in these experiments and will be dealt with in conclusion.

At present it is generally accepted as a law that in nature difference in structure runs parallel with difference in function. The composition of the nucleus reticularis lateralis of at least three parts, differing structurally, would then imply that these parts also differ functionally, *i.e.*, have different connections. It might be supposed that the different types of cells send their axons to phylogenetically and functionally different parts of the cerebellum, *e.g.*, the largest cells in the magno-cellular portion to the anso-paramedian lobule and the lobulus c_2 (the neo-cerebellum), the small cells in the parvi-cellular portion to the vermis of the anterior lobe and the pyramis and uvula (lob. c_1 and b resp.). But, as is evident from the descriptions of the findings presented above, this is not the case. For instance, lesions of each of the parts of the vermis are followed by changes as well in the largest cells in the magno-cellular portion as in the small cells in the parvi-cellular portion, and the borders of the projection areas for the different cerebellar subdivisions coincide only very roughly with the borders between the histologically different parts of the nucleus. Thus it is evident that at least some of the minor parts of the cerebellum (decidedly the di-

visions of the vermis) receive fibers originating from different types of cells, and the explanation of an eventual difference in function of the parts of the nucleus reticularis lateralis cannot be sought for in the distribution to different parts of the cerebellum. On the other hand, one might think of the afferent impulses to the nucleus as a source of difference in function, *i.e.*, the parvi-cellular, the magno-cellular and the subtrigeminal portion receiving fibers from different nuclear complexes. Although nothing can be said concerning this possibility, as these fibers are insufficiently known (*cf.* above), some data may appropriately be mentioned, which tend to minimize this possibility. A condition somewhat similar to that in the nucleus reticularis lateralis system is found in the external cuneate nucleus system. In spite of the fact that this nucleus is composed of cells of different types (*cf.*, for instance, *Brodal 1941*) its afferent as well as its efferent fibers all behave alike, the afferents all have the same origin and the efferents are distributed to the same parts of the cerebellum. Likewise, the several different gray masses constituting the pontine nuclei, as far as is known, receive afferent cortico-pontine fibers of the same type.

Still, this does not imply that no functional significance may be ascribable to the structural differentiation of the nucleus reticularis lateralis. A third possibility still exists, namely: that there is a difference in the type of cerebellar endings of the fibers originating from the different kinds of cells, one kind ending as mossy terminals, the other as climbing fibers. As is well known the opinions of the authors differ widely in regard to the question of the ending of the different afferent cerebellar fiber systems. Thus some investigators hold that the ponto-cerebellar fibers terminate as climbing fibers, whereas others advocate their ending as mossy fibers (for a review of this question, see *Jakob 1928, Ziehen 1934*). Information on this point is gained partly from studies on normal and pathological material, to a lesser extent from experimental investigations with silver methods. But it is very remarkable that in these experimental studies degenerated climbing fibers have not been observed, whereas abundant degeneration of the mossy fibers

has been found. Thus *Miskolczy* described degeneration of the mossy terminals following section of the spino-cerebellar fibers (1931) and likewise after section of the olivo-cerebellar fibers (1934), and *Snider* (1936) observed the same phenomenon after section of the brachium pontis. (Neither had seen degenerated climbing fibers.) According to this the quantitatively most important afferent systems would all terminate as mossy fibers, and it appears that only the vestibulo-cerebellar and perhaps some minor systems (trigemino-cerebellar, reticulo-cerebellar) are left which may reasonably be thought of as the origin of the climbing fibers. As concerns the fibers from the nucleus reticularis lateralis, one is inclined to group these with the olivo-cerebellar fibers, since both systems necessarily will be cut at the same time. Accordingly, the ample occurrence of climbing fibers in the cerebellar cortex as they appear in normal preparations can scarcely be accounted for, and the assumption seems not far-fetched, that the negative results of the experimental studies as concerns these fibers are due to technical difficulties or to special conditions of this type of axonal terminations.¹ If this be so, an explanation is found for the divergent results of the experimental and the other studies of the terminations, and furthermore, nothing excludes the possibility that fibers belonging to one system may terminate partly as mossy fibers, partly as climbing fibers.² If this be the case it seems logical, that fiber systems originating in nuclear masses composed of cells of identical type—as, for instance the inferior olive—may have terminations of one type only, whereas systems arising in complexly built nuclei such as the pontine gray masses and the nucleus reticularis lateralis may be endowed with both types of

¹ Another possibility should also be mentioned. *Lorente de No*, according to *Snider*, regards it possible that the climbing fibers are derived from the cerebellar association fibers.

² *Jakob* (1928), after a review of the data from the literature, is inclined to conclude that all the afferent cerebellar systems partly develop mossy terminals, partly climbing fibers, and that the mode of ending of the different systems takes place only predominantly, and not exclusively, after one of the two principles.

endings, the axons of one or more types of cells ending as mossy terminals, those of other types as climbing fibers. In this way the composition of the nucleus reticularis lateralis of different parts may well be interpreted as an expression of functional difference between the separate parts, as undoubtedly the functional role of the climbing fibers, each linked up probably with only one Purkinje-cell, and of the mossy fibers, so widely distributed in their ending in the granular layer of the cerebellar cortex, must be rather different. It is to be hoped that future research will be able to clear up this question.

SUMMARY

By means of a modified *Gudden* method, worked out by the author, the connections of the nucleus reticularis lateralis with the cerebellum are studied experimentally on a material of 137 rabbits and 87 cats. The distribution of the retrograde cellular changes in the nucleus following circumscribed lesions of the cerebellum are studied in Nissl-stained series, and presented diagrammatically. Owing to the advantages of the method (by which the animals are operated upon at an age of 8-20 days and killed after 6-12 days) it has been possible to determine rather exactly the parts of the nucleus sending fibers to the different parts of the cerebellum.

An introductory description of the nucleus in the rabbit and the cat and the retrograde cellular changes is given.

It is shown that all parts of the cerebellar cortex receive fibers from the homolateral nucleus reticularis lateralis (only as regards the lobulus a, the nodulus, is this not directly demonstrated). The vermis receives a proportionally far greater mass of the fibers than the rest of the cerebellum. Concerning the intra-cerebellar nuclei no conclusions can be drawn.

There is no distinct localization within this projection; nevertheless, certain parts of the cerebellum receive their fibers predominantly from special parts of the nucleus. The parvicellular portion sends its fibers predominantly to the vermal region, the magno-cellular predominantly to the hemispheres

and the subtrigeminal portion to the flocculus and probably the nodulus (the flocculo-nodular lobe). The details in their projection are represented diagrammatically in Figs. 12 and 18 for the rabbit and the cat respectively.

Certain data available from the scanty literature on this topic indicate that the conditions in man are probably similar to those in the experimental animals, but a comparison is made difficult by the lack of sufficient knowledge of the comparative anatomy of the nucleus reticularis lateralis.

The demonstration that all parts of the cerebellar cortex receive fibers from the nucleus does not fit well with the current conceptions of the functional localization within the cerebellum, as the only known afferent fibers to the nucleus are those derived from the antero-lateral column of the spinal cord. However, it is pointed out that the existence of afferent fibers to the nucleus from higher regions of the brain stem cannot be excluded, although such fibers as far as can be seen have not yet been demonstrated. If fibers of this type should be found, the nucleus reticularis lateralis should appropriately be classed with the inferior olive and the pontine nuclei, rather than with the spino-cerebellar systems.

Finally the problem is discussed, whether the organization of the nucleus in several parts differing structurally can be regarded as an expression of a functional difference of the separate parts. It is hinted that the difference may be correlated with a difference in the type of the axone endings in the cerebellar cortex, some cell types being endowed with mossy terminals, others with climbing fibers.

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ADDENDUM:

VRAA JENSEN in his recent work: The motor nucleus of the facial nerve, Copenhagen 1942, discusses the connections of the nucleus reticularis lateralis. Unfortunately his monograph came into my hands after this manuscript was submitted for publication and thus could not be considered here.

EINE THEORIE ÜBER DIE NATUR DER GEFÜHLE UND EIN VORSCHLAG ZUR THERA- PIE DES MANISCH-DEPRESSIVEN IRRESEINS

VON
GUNNAR DAHLBERG

Den ersten ernsthaften Versuch, die Natur der Gefühle zu analysieren stellt die Theorie von *Lange* und *James* dar. Unabhängig voneinander und ungefähr zur gleichen Zeit wiesen sowohl *Lange* (1885) als auch *William James* (1884) darauf hin, dass die Gefühle als wesentliches Moment körperliche Sensationen enthalten. *Lange* hob hervor, dass Gefühle mit Kreislaufveränderungen einhergehen. Das Herz schlägt langsamer oder schneller, man errötet oder wird blass u. s. w. Derartige Sensationen gelangen zum Gehirn, und das Bewusstwerden solcher Sensationen ist ein sehr wichtiger Bestandteil eines Gefühles. *James* führte denselben Gesichtspunkt an, machte aber weniger spezielle Annahmen. Er nahm nur an, dass körperliche Sensationen, unabhängig davon, ob sie sich auf den Kreislauf oder andere Prozesse beziehen, einen wesentlichen Bestandteil eines Gefühles darstellen. Es ist üblich, die paradoxe Zuspitzung, die *James* seiner Theorie gab, zu zitieren; er hob nämlich hervor, dass man deswegen ängstlich sei, weil man zittert, man zittere aber nicht deswegen, weil man ängstlich ist. Der Schwerpunkt der Überlegung ist, dass, falls man sich vorstellt, von einem starken Gefühl die körperlichen Sensationen entfernen zu können und z. B. bei einer erschreckten Person das Herz ruhig schlagen, die Muskulatur normal funktionieren lässt, dann von dem Gefühl nichts anderes übrig bleiben würde als eine blasse intellektuelle Vorstellung, dass irgend eine Gefahr droht.

James hebt hervor, dass bei der Diskussion der Theorie mit verschiedenen Personen die meisten der Ansicht waren, eine solche Abstraktion ausführen zu können, und zu demselben Ergebnis kamen wie er selbst. Andere erklärten, dass sie sich die Entfernung der körperlichen Sensationen nicht vorstellen könnten — sie verstanden nach *James* die Frage nicht. Beide Autoren haben bei der Ausarbeitung ihrer Theorien einen vorurteilsfreien Scharfsinn entwickelt, und beide waren sich völlig klar darüber, dass sich die Anschauung auf den ersten Blick als unberechtigt darstellen muss. *James* schliesst seinen kurzen Artikel mit der Erklärung, dass das beste, was man über seine Theorie sagen kann, ist, dass er selbst beim Schreiben seines Artikels fast von ihrer Richtigkeit überzeugt wurde. Anfänglich kam es gegen die Theorie zu einer indignierten Opposition, die allmählich abklang; sie wird immer noch als Versuch einer Erklärung besprochen, der sich nicht als völlig unberechtigt ablehnen lässt.

Eine andere Theorie wurde zuerst von *Dana* (1921) angedeutet und später unabhängig von ihm von *Cannon* (1927) aufgestellt und eingehender ausgearbeitet. Nach dieser Theorie sollen die Eindrücke und intellektuellen Prozesse, die gefühlsmässige Reaktionen bewirken, zunächst einen Impuls in gewisse Zentren im Boden des Grosshirns (Thalamus) schicken. Von diesen Zentren sollen teils Impulse in periphere Organe ausgehen, die Kreislaufveränderungen und ähnliches bewirken, teils sollen gleichzeitig Impulse in die Gehirnrinde gesandt werden; diese sekundären Impulse sollen ein Gefühl veranlassen. (Derartige sekundäre Impulse sollen auch entstehen können, wenn ein Reiz von einem peripherischen Sinnesorgan die zentralen Kerne auf dem Weg in die Rinde hinauf passiert.) Auch für diese Anschauung konnten keine zwingenden Beweise vorgelegt werden. Bei der Besprechung seiner Theorie hebt *Cannon* Einwände hervor, die man gegen die Theorie von *Lange* und *James* erheben kann, die aber nicht die von ihm aufgestellte Ansicht treffen.

Tierexperimente haben gezeigt, dass Tiere, bei welchen die Verbindungen zwischen dem Nervensystem und dem übrigen Körper operativ zerstört wurden, dennoch ihren Gefühlen, z. B.

Zorn und Freude, Ausdruck geben können. Gegen diese Versuche ist vor allem einzuwenden, dass man die Verbindung zwischen dem Nervensystem und dem übrigen Körper niemals vollständig aufheben kann. Kann ein Tier seine Gefühle ausdrücken, so müssen ja bestimmte Verbindungen erhalten geblieben sein. Wären alle Verbindungen aufgehoben, so würde man ja keineswegs wissen können, ob das Tier irgendwelche Gefühle hat. Ausserdem kann hervorgehoben werden, dass man nicht sicher weiss, ob das operierte Tier Gefühle besitzt. Man muss ja mit eingearbeiteten Gewohnheiten rechnen, auf bestimmte Eindrücke auf eine besondere Art zu reagieren. Das freudig erkennende Lächeln, mit welchem viele Personen auch gleichgültige Bekannte grüssen, stellt selbstverständlich keineswegs immer einen Gefühlsausdruck dar. Konventionelle Reaktionen dieser Art weisen mitunter eine Nuance von etwas Mechanischem und Leblosem im Ausdruck selbst auf. Es ist selbstverständlich unmöglich, bei Versuchstieren solche Nuancen zu unterscheiden. Es kann sich dabei mit anderen Worten um bedingte Reflexe gehandelt haben.

Gegen die Theorie von *Lange* und *James* wurde ferner eingewandt, dass Gefühle verschiedenen Charakters ziemlich gleichartige körperliche Reaktionen auslösen, und dass das Hervorrufen körperlicher Reaktionen einer bestimmten Art keine entsprechenden Gefühle bewirkt. Gegen beide Einwände kann man jedoch anführen, dass unsere Kenntnisse über die körperlichen Reaktionen, welche die Gefühle begleiten, ziemlich beschränkt sind, und dass wir nicht entscheiden können, ob Unterschiede vorhanden sind, von denen wir nichts wissen. Dasselbe gilt für den Einwand, dass innere Organe bei Eingriffen gefühlslos sind. Man kann bei Patienten in Lokalanästhesie in den Darm einschneiden oder ihn klemmen, ohne dass er etwas fühlt, obwohl er bei vollem Bewusstsein ist. Es ist indessen klar, dass diese Form der Gefühllosigkeit nicht viel mit dem Problem zu tun hat. Ohne Zweifel haben wir bei starken Gefühlen Sensationen von Seiten der inneren Organe, und bei Erkrankungen fühlen wir im übrigen auch Schmerzen in diesen Organen.

Schliesslich wurde hervorgehoben, dass die körperlichen Re-

aktionen zu langsam auftreten, um der wesentliche Bestandteil eines Gefühls sein zu können. Das Gefühl tritt früher auf. Hierbei ist es aber nicht möglich, etwas Bestimmtes zu behaupten, da es schwer ist, den Zeitpunkt des Auftretens eines Gefühles zu bestimmen.

Ein Einwand, den man gegen die Theorie von *Dana* und *Cannon* zu erheben versucht ist, besteht darin, dass man deutliche Störungen des Gefühlslebens bei Schädigungen der zentralen Gehirnteile finden müsste, wie sie zum Beispiel bei Gehirnentzündung (Encephalitis) auftreten. Derartige sichere Störungen konnten aber nicht festgestellt werden. Ferner müsste man bei Störungen im Gefühlsleben wenigstens mitunter Schädigungen in den zentralen Gehirnteilen finden, die eine entscheidende Rolle für die Entstehung gefühlsmässiger Reaktionen spielen würden. Auch solche konnte man bisher nicht feststellen.

Ich habe oben angeführt, dass es schwer ist zu bestimmen, wie lange es dauert, bis ein Gefühl entsteht. Erhält man eine traurige oder eine freudige Nachricht, so steht man nicht mit der Uhr in der Hand da und bestimmt die Zeit, bis man traurig oder fröhlich wird. Tierversuche geben kaum zufriedenstellende Ergebnisse, da es, wie bereits erwähnt, sehr schwer ist, reflexmässige Reaktionen von wirklichen gefühlsmässigen Reaktionen abzutrennen. Die zahlenmässigen Angaben, die zu erhalten waren, dürften deswegen von diskutablen Wert sein. Es dürfte indessen kein Zweifel darüber bestehen, dass gefühlsmässige Reaktionen wesentlich langsamer verlaufen als rein intellektuelle Prozesse. Wird man von einer Person plötzlich und unerwartet beleidigt, so wird man nicht sofort ärgerlich. Es vergeht eine kurze Zeit. Man sagt, dass man versteht, was geschehen ist, man begreift es aber nicht richtig. Der intellektuelle Prozess verläuft blitzschnell. Das Gefühl tritt allmählich auf und wird erst nach einiger Zeit sehr stark. Entdeckt man in diesem Zeitpunkt, dass das Ganze auf einem Missverständnis beruhte, und dass keine Absicht zur Beleidigung bestand, so verschwindet der Zorn nicht augenblicklich. Man ist noch eine Zeitlang erregt, und dies kommt dadurch zum Ausdruck, dass man immer noch nach einem Anlass sucht. Man sagt vielleicht, der Be-

treffende habe sich plump ausgedrückt, und es sei sein Fehler, dass ein Missverständniss entstand. In einer gefährlichen Situation kann man verstehen, worum es sich handelt, und dementsprechend handeln. Die emotionelle Reaktion tritt vielleicht erst dann ein, wenn die Gefahr vorüber ist, und wenn für sie kein Anlass mehr vorliegt. Es besteht also ein wichtiger Unterschied einerseits zwischen der blitzschnellen Geschwindigkeit, mit welcher man einen Eindruck erfasst, und andererseits der relativen Langsamkeit, mit welcher gefühlsmässige Reaktionen auftreten.

Eine andere ebenfalls wohlbekannte Erscheinung besteht darin, dass gefühlsmässige Reaktionen auf chemischem Weg erzeugt werden können. Eine Anzahl von Substanzen, von welchen der Alkohol wohl am besten bekannt ist, haben das Vermögen, eine veränderte Gefühlslage hervorzurufen. Unter dem Einfluss des Alkohols wird man zuerst lustig. Ist diese Wirkung abgeklungen, so kann man deprimiert werden und eine grössere oder geringere Neigung zu unmotivierten Zornesausbrüchen erhalten. Gefühle, die auf chemischem Weg hervorgerufen werden, müssen ja in erster Linie darauf beruhen, dass das Blut einen bestimmten Gehalt irgend einer Substanz aufweist, die entweder direkt auf die Gehirnrinde oder auf andere Organe wirkt, die ihrerseits die Rinde beeinflussen. In Übereinstimmung mit der Theorie von *Lange* und *James* kann man annehmen, dass solche Substanzen Veränderungen der inneren Organe, des Kreislaufes und von ähnlichem bewirken, und dass es diese Veränderungen sind, die in der Gehirnrinde als Gefühl aufgefasst werden. Man kann ferner annehmen, dass die chemischen Substanzen das Gehirn entweder nach *Dana* und *Canon* in untergeordneten zentralen Teilen oder die Gehirnrinde selbst beeinflussen, und dass die Wirkung, die im Gehirn entsteht, als ein Gefühl aufgefasst wird.

Es ist auch eine dritte Möglichkeit vorhanden. Lassen sich Gefühle auf chemischem Wege hervorrufen, so kann man sich ja auch vorstellen, dass normale Gefühle durch chemische Veränderungen im Blute bedingt werden. Man kann sich die Möglichkeit vorstellen, dass bestimmte Eindrücke und bestimmte Vorstellungen Gefühle auf die Weise hervorrufen, dass vom

Gehirn zu den endokrinen Organen Impulse gesandt und dass von diesen Substanzen in das Blut ausgeschieden werden. Diese Substanzen beeinflussen ihrerseits das Gehirn. Aus diesem Grunde dauert es eine Zeit, bis ein Gefühl allmählich die maximale Stärke erreicht. Alkohol kann auf die Weise wirken, dass die Substanz in erster Linie bestimmte endokrine Organe reizt, man kann sich selbstverständlich aber auch vorstellen, dass in erster Linie bestimmte Gehirnzentren beeinflusst werden, und dass diese sekundär Impulse zu den hypothetischen endokrinen Organen senden. Schliesslich besteht ja auch die Möglichkeit, dass der Alkohol direkt ähnliche Wirkungen hat wie die hypothetischen Hormone.

Ein Einwand, der auch gegen diese Theorie erhoben werden kann, ist der, dass Veränderungen im Gehalt des Blutes an bestimmten Substanzen vielleicht nicht ausreichend schnell erfolgen können, um der Geschwindigkeit zu entsprechen, mit welcher Gefühle entstehen und abklingen. Da es sich um hypothetische Substanzen und Ausscheidungen handelt, besteht ja keine Möglichkeit, sich über diesen Punkt endgültig auszusprechen. Es sei indessen daran erinnert, dass bereits *James* hervorhebt, dass einfache Sensationen direkt behaglich oder unbehaglich sein können, und dass man diese Qualitäten der Sensationen von Emotionen, Gefühlen, abtrennen muss. Sensationen können also primär lust- oder unlustbetont sein, Emotionen sind aber etwas Sekundäres.

Ein Unterschied zwischen den beiden früheren Theorien und meiner Theorie besteht nun darin, dass es verhältnismässig leicht ist zu entscheiden, ob meine Theorie einigermaßen richtig ist, während es hingegen sehr schwer ist, den Richtigkeitsgrad der beiden anderen Theorien zu prüfen.

Bei manisch-depressivem Irresein ist ja eine sehr starke Veränderung des Gefühlslebens vorhanden. Eine manische Person ist krankhaft fröhlich; eine Person in depressiver Phase hingegen ist krankhaft traurig. Wird die Gefühlslage durch Substanzen bedingt, die im Blute vorhanden sind, so müsste man ja durch Austausch einer bestimmten Blutmenge von einer Person in manischer Phase auf eine Person in depressiver Phase

(oder umgekehrt) die Stimmungslage ausgleichen können. Vor 9 Jahren führte ich ein solches Experiment aus, leider war es aber nicht möglich, mehr als einen halben Liter Blut zu überführen. Es handelte sich um einen ersten Versuch; ich erachtete es deswegen als am besten, nur einen kleinen Eingriff vorzunehmen.

Der Versuch wurde bei folgenden Patienten vorgenommen: Patient Nr. 1, I. A., ein jüdischer Schneider, geb. 1879, der seit 1924 unter fünf Perioden mit der Diagnose Psychosis manico-depressiva aufgenommen worden war. Er wurde am 30. November 1932 zum 6. Mal in das Krankenhaus Långbro aufgenommen. Er wies damals ausgeprägte manische Symptome auf und musste auf der Unruhigen-Abteilung gehalten werden.

Patient Nr. 2, J. O., ein Beamter, geb. 1885, der früher einmal wegen manisch-depressiven Irreseins aufgenommen war. Er wurde erneut am 18. Oktober 1932 mit der Diagnose Psychosis manico-depressiva aufgenommen und wies das Bild einer ausgeprägten Depression auf.

An beiden Patienten wurden vor der Bluttransfusion die üblichen Untersuchungen ausgeführt. Am 21. August 1933 wurde eine Transfusion von 500 g Blut des manischen Patienten (Nr. 1) auf den deprimierten Patienten (Nr. 2) vorgenommen. Letzterer war angesichts der Vorbereitungen zur Operation sehr ängstlich und unruhig. Auch der manische jüdische Schneider wurde etwas düster, als er auf den Operationstisch gelegt wurde und fragte, um was es sich handle. Als ich ihm erklärte, dass wir nur eine kleine Blutmenge entnehmen wollten, die wir brauchten, um dem Patienten auf dem anderen Operationstisch zu helfen, und ihn fragte, ob er etwas dagegen habe, antwortete er: »Durchaus nicht. Wir sind gewohnt, unser Blut zu geben.«

Irgend eine Wirkung der Blutüberführung erfolgte indessen nicht. Der deprimierte Patient wurde ein wenig ruhiger, dies dürfte aber am ehesten damit zusammengehangen haben, dass die verhältnismässig einfache Operation glücklich überstanden war. (Der manische Patient wurde ebenfalls ruhiger, so dass er eine Zeitlang auf der Ruhigen-Abteilung gehalten werden konnte.) Das Experiment hatte also ein negatives Ergebnis. Man

muss sich aber daran erinnern, dass nur etwa 10 % der totalen Blutmenge übergeführt wurden, und es ist sehr wohl möglich, dass dies zu wenig war, um eine Wirkung zu erzielen. Es ist deswegen wünschenswert, dass das Experiment in grösserem Ausmass wiederholt wird. Ich habe keine Möglichkeit dies zu tun. Mir bleibt nur die Hoffnung, dass sich jemand anders dafür interessiert, die Untersuchung weiterzuführen.

Im Hinblick auf die naheliegende Frage, wie viel Blut übergeführt werden kann, will ich daran erinnern, dass in älteren Zeiten sehr oft Aderlässe ausgeführt wurden, wobei grosse Blutmengen abgelassen wurden. Es war nichts Ungewöhnliches, während des Verlaufes einer Lungenentzündung insgesamt 5 Liter Blut abzulassen. Man dürfte ohne Gefahr ein bis zwei Liter und vielleicht mehr austauschen können. Man weiss zwar nicht, wie beständig die Substanzen sind, die ev. im Blut vorhanden sind und für Gefühlsreaktionen Bedeutung haben; aber sicher sind sie nicht während einer längeren Zeit beständig. Es ist deshalb wünschenswert, dass die Blutüberführung schnell vorgenommen wird, und es wäre vermutlich vorteilhaft, wenn sie unmittelbar durch direkte Verbindung des Spenders mit dem Empfänger ausgeführt würde.

Im Hinblick auf die Substanzen, die eventuell im Blute vorhanden sind, bestehen zwei Möglichkeiten. Eine fröhliche Stimmung kann mit dem Überschuss an irgend einer Substanz und eine traurige Stimmung mit einem Defizit an einer solchen oder umgekehrt zusammenhängen. Weniger wahrscheinlich ist die andere Möglichkeit, dass die frohe und die traurige Stimmung von verschiedenen Substanzen herrühren. Man kann nicht gleichzeitig froh und traurig sein, was möglich wäre, falls es sich um zwei Substanzen handelte.

Ich habe es vermieden, die endokrine Theorie über die Entstehung von Gefühlen vom psychologischen Gesichtspunkt aus näher zu besprechen. Nachdem man Versuche ausführen kann, ist es ja nicht notwendig die theoretische Seite eingehender zu behandeln, wie das erforderlich ist, wenn man die Theorie nur auf psychologischen Beobachtungen aufbauen muss. Um aber

diese Seite des Problems nicht völlig ausseracht zu lassen, seien in aller Kürze einige Gesichtspunkte angeführt.

Man weiss jetzt, dass die Sexualität endokrin bedingt ist. Sie erwacht nicht eher zu ihrer vollen Stärke, als bis die Geschlechtsdrüsen eine solche Entwicklung erreicht haben, dass sie in grösserem Ausmasse Hormone in das Blut ausscheiden. Die Sexualität verschwindet, wenn die Hormonausscheidung aufhört, und die Gefühle, welche mit der Sexualität zusammenhängen, erhalten einen anderen Charakter. Es besteht ja ein Unterschied zwischen der sexuell betonten Liebe und einer Liebe, die den Charakter der Zuneigung trägt. Man kann bei Tieren mit Hilfe von Sexualhormonen Sexualität hervorrufen. Bei Kaninchen wurde festgestellt, dass ein Zusammenspiel zwischen dem Nervensystem und der Ausscheidung der Sexualhormone vorhanden ist. Reifen die Eier in den Eierstöcken des Kaninchens, so kommt es nur dann zu einem Zerreißen der Blasen, worin die Eier liegen, wenn eine Paarung stattfindet. Nach einer Paarung zerreißen die Eiblasen schnell, was damit zusammenhängen dürfte, dass die nervösen Sensationen bei der Paarung die Hypophyse beeinflussen, so dass diese eine erhöhte Menge Eireifungshormon (Prolan A) ausscheidet. Die schnell zunehmende Ausscheidung dieses Hormons bewirkt, dass die Eier in den Eierstöcken schnell reifen, so dass die Eiblasen springen. Dies zeigt, dass die Hormonausscheidung durch das Nervensystem reguliert werden kann. Die Sexualhormone sind ferner von Bedeutung für die Entstehung der Gefühle, die mit der Sexualität zusammenhängen. Wie die Hormone wirken, ist noch nicht ermittelt. Die Hormone können eine Bereitschaft zur Reaktion auf bestimmte Sensationen hervorrufen. Ist der Hormongehalt des Blutes hoch, so bedingen Sensationen, die einen sexuellen Charakter haben, eine starke Veränderung der Gefühlslage. Ist der Hormongehalt niedrig, so haben die Sensationen keinen oder einen unbedeutenden Effekt. Man kann sich vorstellen, dass die Hormone auf dieselbe Weise bei manisch depressivem Irresein eine Neigung hervorrufen, in froher oder trauriger Richtung zu reagieren. Wie die Hormone wirken, ist, wie bereits hervorgehoben, unklar, und man kann sich ja auch

vorstellen, dass Mechanismen nach *Dana* und *Cannon* wie nach *Lange* und *James* ebenfalls eine Rolle spielen können. Der Mechanismus der Gefühle ist nicht notwendigerweise so einfach, dass man ihn nur auf eine Weise erklären kann. Die Theorie, welche ich aufgestellt habe, kann eine gewisse Tragkraft haben, ohne alles zu erklären; ebenso wie *James* will ich nur soviel behaupten, dass es mir gerade gelungen ist, mich selbst davon zu überzeugen, dass es wert ist, die Theorie zu veröffentlichen und zu prüfen. Es dauerte neun Jahre, ehe ich so weit kam.

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ÜBER DIE ANOSOGNOSIE

VON

RING LUNDQUIST

Der Begriff der Anosognosie wurde zum ersten Mal von *Babinski* eingeführt. *Babinski* (1914) bezeichnete als Anosognosie (A.) das Phänomen, dass ein Patient mit einer linksseitigen Hemiplegie sich dieses somatischen Defektes nicht bewusst wird. Diese ursprüngliche Definition von *Babinski* ist später für zu eng und nicht zweckmässig gehalten worden, und nachdem man über die hierzu gehörenden Phänomene gemacht grössere Erfahrung hatte, wurde auch der Begriff der A. erweitert, so dass er die mit der A. nahe verwandten Zustände ebenfalls umfasst. Ob eine derartige Erweiterung des Begriffes berechtigt ist, kann man bezweifeln. Rechnet man nämlich die Depersonalisationsphänomene noch zu der A., so bedeutet dies, dass man für sie dieselbe Genese annimmt, was jedoch keineswegs sicher ist. Die Grenzen des Begriffes als solcher sind von einigen Verfassern völlig durchbrochen worden, die überhaupt alle Fälle mit einer mangelhaften Krankheitseinsicht zur A. rechneten, während andere dagegen in der A. nur ein Teilsymptom einer grösseren Krankheitsgruppe sehen wollten. Die Unklarheit über die Abgrenzung des Begriffes führte zu sichtlichen Schwierigkeiten bei der Klärung der Ursache der A. Beschäftigt man sich mit dieser Frage, so muss man deshalb genau angeben, was man als A. bezeichnet.

Wenn ich im folgenden von einer A. spreche, so verstehe ich darunter das Phänomen, dass ein Hemiplegiker seinen Defekt nicht erlebt. Dieser Zustand ist als A. »im engeren Sinne« be-

zeichnet worden. Von der ursprünglichen Definition *Babinskis* unterscheidet sich die meinige dadurch, dass sie sich nicht nur auf die linksseitige Hemiplegien beschränkt, und dass der Begriff des Erlebens eingeführt wird, um die Art der Störung besser zu veranschaulichen.

Der Grund, warum ich meine Definition nicht nur auf linksseitige Hemiplegien beziehe, ist darin zu suchen, weil dies falsch wäre. In der schwer zu überblickenden kasuistischen Literatur habe ich nämlich drei Fälle von A. bei Ausfallssymptomen der rechten Körperhälfte gefunden, von denen wenigstens zwei, die Fälle von *Wagner* und *Zillig*, vollkommen eindeutig sind, während der dritte, von *Stertz*, nur kurz berührt wird. Ausserdem kann ich zu dieser Kasuistik von »rechtsseitigen A.-Fällen bei Rechtshändern« einen weiteren Fall hinzufügen. Der Umstand, dass die linksseitigen Fälle soviel häufiger sind, bildet noch ein ungelöstes Problem. Bevor die rechtsseitigen Fälle bekannt waren, schrieb z. B. *Pötzl* der rechten Gehirnhälfte eine besondere Bedeutung für »das Körperschema« zu, mit dessen Hilfe er die A. erklären wollte. *Hauptmann*, der keine rechtsseitigen Fälle kannte, zweifelte an der besonderen Bedeutung der rechten Gehirnhälfte und suchte die Erklärung in einer Schädigung des Corpus callosum. Der schwedische Neurologe *Barkman*, der die A. eingehend untersuchte, wies schon im Jahre 1925 darauf hin, dass die Tatsache, dass die A. nur bei linksseitigen Hemiplegien beschrieben worden ist, kein Beweis dafür sei, dass die A. ausschliesslich mit Läsionen der rechten Hemisphäre zusammenhänge. B. nahm an, dass eine schwere Schädigung der linken Hemisphäre, die zu einer A. führt, auch eine starke Aphasie bedingen müsse, die die Feststellung des psychischen Zustandes des Patienten unmöglich macht. Wie man jetzt feststellen kann, hatte *Barkman* also teilweise recht. Seiner Ansicht hatte sich u. a. *Waldenström* angeschlossen.

Lunn veröffentlichte 1941 eine Arbeit über die A. und die mit dieser verwandten Zustände und stellte dabei, von der Birnbaumschen Strukturanalyse ausgehend, eine Theorie zur Erklärung des sog. Antonschen Syndroms auf. An einigen Stellen seiner Arbeit erwähnt er, dass die A. nur bei linksseitigen Hemiplegien

beschrieben worden ist, und er zieht daraus — an und für sich bedeutungslos — den falschen Schluss, dass die Voraussetzung für das Auftreten einer A. eine genau lokalisierte anatomische Destruktion ist, die bei der Hemiplegie das Symptom nur hervorrufen zu können scheint, wenn die nicht dominante Hemisphäre geschädigt wird.

Ich hielt es für notwendig, die Unrichtigkeit der früher allgemein angenommenen Anschauung, dass eine A. nur bei linksseitigen Hemiplegien auftritt, hervorzuheben, da gerade sie gewissen Überlegungen über die Lokalisation zugrundegelegt worden ist (*Pötzl*).

Ferner habe ich den Begriff des Erlebens in die Definition eingeführt, weil er — wie oben erwähnt — die Art der Störung veranschaulichen kann. Dass der Kranke seinen Defekt nämlich nicht erfährt, hängt mit dem bewussten Erleben zusammen und ist also etwas Subjektives. In diesem Zusammenhang will ich jedoch nicht näher auf die Frage eingehen, sondern nur vorausschicken, dass der unten vorgenommene Versuch, die A. zu erklären, teilweise auf den Prinzipien, die von *Sjöbring* über die Art des Erlebens aufgestellt wurden, aufbaut.

Die A. ist kein gar zu seltenes Vorkommnis. Ursprünglich wurde sie mehr oder weniger für eine Kuriosität gehalten. In letzter Zeit hat man ihr jedoch allmählich mehr Interesse gewidmet. Die hängt offenbar damit zusammen, dass man durch die A. über die anatomische Grundlage gewisser psychopathologischer Zustände Aufschluss zu gewinnen hoffte. Die A. hat also in dem alten Streit zwischen den Vertretern der Lokalisationslehre und ihren Gegnern eine grosse Rolle gespielt. Auch für einige rein psychologische Probleme ist sie von Bedeutung gewesen. Sie ist sicher wesentlich häufiger, als man für gewöhnlich annimmt. Für denjenigen, der längere Zeit auf einer internen Station, die stark mit akuten Hemiplegien belegt ist, gearbeitet hat, bedeutet sie keine Seltenheit. Sie wird jedoch keineswegs immer diagnostiziert. Dies beruht offenbar darauf, dass man an sie nicht oft genug denkt. Sie ist nämlich nicht immer ohne weiteres zu bemerken. In den letzten Jahren wurden in Skandinavien (*Waldenström*, *Lunn*) mehrere Fälle von A. veröffentlicht.

Da diese alle »linksseitig« waren, erscheint es mir von Interesse, einen »rechtsseitigen« Fall hinzufügen, über den ich kurz berichten will. Ein weiterer Grund dafür, diesen Fall zu publizieren, ist, weil er bisher der einzige »rechtsseitige« ist, bei dem eine Sektion vorgenommen wurde. Er erscheint deshalb besonders aufschlussreich für die grobe, der A. zugrunde liegenden Schädigung.

A. J., eine 62-jährige Frau, wurde am 1.2.1941 in die I. Medizinische Abteilung des Sahlgrenschen Krankenhauses aufgenommen. In den letzten Tagen vor der Einlieferung hatte sie etwas Kopfschmerzen gehabt, war aber im übrigen immer gesund gewesen. Rechtshänder (schrieb, nähte, stopfte Strümpfe usw. mit der rechten Hand und benutzte niemals die linke Hand zu Arbeiten, die ein Rechtshänder mit der rechten Hand auszuführen pflegt). Am Aufnahmetage sank die während ihrer Arbeit zu Boden. Sie wollte nicht glauben, dass sie besinnungslos gewesen sei. Bei der Aufnahme in das Krankenhaus war sie bei Bewusstsein und ganz gut orientiert. Ihr Allgemeinzustand war etwas beeinträchtigt. Sie hatte andauernd Schlucken, klagte über Kopfschmerzen, sprach fast ununterbrochen, manchmal zusammenhängend, aber dann auch wieder völlig unverständlich.

Bei der körperlichen Untersuchung, abgesehen von einem erhöhten systolischen Blutdruck von 250 mm Hg, kein besonderer Befund der inneren Organe. Wassermann im Blut neg.

Bei der Ophthalmoskopie war der rechte Augenhintergrund o. B., der linke konnte nicht beobachtet werden, da die Patientin dieses Auge zukniff. Nach einer groben Untersuchung erhielt man den Eindruck, dass eine rechtsseitige Hemianopsie vorhanden war. *Déviatiou conjugué*e nach links. Rechtsseitige Facialis-, Gaumen- und Zungenparese. Bewegt den rechten Arm nicht, kleine Bewegungen mit dem rechten Bein auf Aufforderung. Beim Schlucken keine Nabeldeviation. Reagiert nicht auf Nadelstiche auf der rechten Gesichtshälfte. Sticht man in den rechten Arm, so wird dieser etwas bewegt. Reaktion auf Nadelstiche in das rechte Bein und die rechte Rumpfhälfte. Tiefensensibilität nicht untersucht. Pupillenreaktion o. B. Bauchdeckenreflexe

rechts etwas schwächer als links, Sehnen und Periostreflexe der Extremitäten o. B. Babinski auf beiden Seiten positiv.

Ihr psychischer Status war folgender: Sie lässt sich nur ungern untersuchen, meint, dass man sie unnötig plage und sie daran hindere Wasser zu trinken. Die spontane Sprache manchmal verständlich, manchmal vollständig unverständlich. Sie antwortet meist adäquat auf Fragen, manchmal aber völlig sinnlos. Auf die Frage, ob sie Rechts- oder Linkshänder sei, antwortet sie: »Wir werden die Sache schon machen«. Sie ist zeitlich nicht orientiert. Auf die Frage, welcher Wochentag es sei, antwortet sie: »Es ist der 16. heute«. Sie scheint sich ihrer Parese überhaupt nicht bewusst zu sein und glaubt, den rechten Arm ebenso gut wie den linken zu bewegen. In den folgenden Tagen war sie sehr schläfrig, zeitlich und räumlich desorientiert, und ihre Sprache zeigte aphatische Störungen. Die Hemiplegie bestand am 6.2. in einer Lähmung des rechten Armes und Beines. Sie war hemihypästhetisch und hatte eine rechtsseitige Hemianopsie. Von ihrer Hemiplegie wusste sie nichts und versicherte, dass sie den rechten Arm und das rechte Bein auf die Aufforderung hin bewege — obwohl sie tatsächlich unbeweglich dalagen. Patellar- und Achillessehnenreflex rechts nicht auslösbar. Babinski immer noch auf beiden Seiten positiv. Ophthalmoskopisch zeigte sich über beiden Papillen ein leichtes Ödem. Am 14.2. konnte sie das rechte Bein etwas bewegen, der übrige somatische Status war unverändert. Die A. begann zu verschwinden. Am 20.2. wurde die Patientin in das Vasa-Krankenhaus (für chronische Fälle) verlegt. Folgende Angaben stammen aus der dortigen Krankengeschichte: 11.4. In der letzten Zeit psychisch stärker verändert. Klagt heute über Stechen links in der Brust. Immer noch schlaffe rechtsseitige Hemiplegie. Rechts Babinski pos. 14.4. Exitus letalis.

15.4. Obduktion (cand. med. Olof Olsson) Pathol.-anatom. Diagnose: Haemorrhagia cerebri. Arterionephrosklerose. Cor hyperton. Thrombosis ven. hypogastr. dext. Embolia pulmonum.

Gehirn: Duraldruck nicht erhöht. Basale Hirngefäße stark verkalkt. In der linken Hemisphäre, von der hinteren Kante des Linsenkernes, in der weissen Substanz lateral vom Thalamus

bis zur Umbiegung des Lateralventrikels in den Temporallappen eine ältere Blutung, die anfängt, sich in eine Zyste zu verwandeln. In der Zyste nekrotisches Gewebe und koaguliertes Blut, das stark in Hämatin umgewandelt ist.

Die Untersuchung der übrigen Organe ergab Veränderungen, auf Grund deren die oben angegebene pathologisch-anatomische Diagnose gestellt wurde.

Zusammenfassung der Krankengeschichte: Eine vorher gesunde 62-jährige Frau erkrankt plötzlich an einer Haemorrhagia cerebri mit einer rechtsseitigen Hemiplegie, rechtsseitigen Hemianopsie und A. 6 Wochen danach stirbt sie an einer Lungenembolie, die durch eine Thrombose der Vena hypogastrica dextra hervorgerufen wurde. Bei der Obduktion findet man eine ältere Blutung in der linken Hemisphäre.

In bezug auf die cerebrale Erkrankung der Patientin machte die Diagnose hier keine Schwierigkeiten. Die A. war deutlich ausgeprägt. Ausserdem zeigte die Patientin eine Form der Aphasie, die am ehesten zu der sog. sensorischen Aphasie zu rechnen ist. Es war also eine Kombination einer A. und einer Aphasie wie bei *Zilligs* Fall vorhanden.

Das Wesen der A. ist auf drei verschiedene Weisen gedeutet worden.

1. Die Ursache seien die Sensibilitätsstörungen, die gleichzeitig mit den Paresen auftreten. Diese Theorie wird u. a. von *Barré* vertreten, der den Verlust der Tiefensensibilität bei intakter Oberflächensensibilität für den wesentlichen Punkt hält. Derselben Ansicht war schon *Babinski*, der sich jedoch nicht ganz darauf festlegt. Die Theorie von Waldenström ist ähnlich, wenn auch genauer ausgearbeitet. Auf die Einzelheiten kann hier nicht näher eingegangen werden, und es sei deshalb auf die Originalarbeit verwiesen. Für alle diese Theorien gilt jedoch, dass sie nicht erklären können, warum nicht alle Fälle mit derartigen Sensibilitätsstörungen eine A. verursachen.

2. Die Ursache der A. sei eine Läsion des organischen Substrates des sog. »Körperschemas«. Diese Theorien gehen von denen über das sog. Körperschema aus. Nach *Hauptmann* ist »das Bewusstsein des eigenen Körpers, das sog. »Körperschema«, eine

Funktion der im Gehirn niedergelegten sensiblen und optischen Engramme«. Damit z. B. das Dasein und die normale Funktion einer Extremität bewusst wird, müssen neue sensible und optische Eindrücke in das »Körperschema« eingeführt werden und die alten Engramme »decken«. Kommt es nun nicht zu einer Kongruenz zwischen den neu eingeführten Eindrücken und den alten Engrammen, wie z. B. bei einer Armlähmung, bei der nach dem Erleben des Willensimpulses zur Bewegung der Eindruck der Bewegung des Armes ausbleibt, so bedeutet dies psychisch das Erleben, dass der Arm gelähmt ist. Kommt dieses Erleben nicht zustande, wie bei der A., so beruht dieses auf einer Zerstörung des organischen Substrates für das »Körperschema«. Diese Theorie zur Erklärung der A. ist von *Lunn* — m. E. mit Recht — kritisiert worden. *Lunn* sagt u. a. »Die Leichtigkeit, mit der die Lokalisation des für das »Körperschema« essentiellen organischen Substrates je nach dem Sektionsbefund geändert werden kann, veranschaulicht die prinzipielle Dehnbarkeit des Begriffes, die dessen tatsächliche Wurzel mehr als zweifelhaft erscheinen lässt«. Mein oben mitgeteilter Fall bestätigt diese Auffassung von *Lunn* und zeigt gleichzeitig die Unrichtigkeit der Annahme von *Pötzl* über die besondere Bedeutung der rechten Gehirnhälfte für die Lokalisation des »Körperschemas«. Andererseits kann das Sektionsresultat meines Falles als eine Stütze für *Hauptmanns* Theorie über die genetische Bedeutung der Balkenschädigungen für die A. angesehen werden. Es sind jedoch zahlreiche Balkenschädigungen ohne A. beschrieben worden, und daher genügt auch diese Theorie nicht um dem Problem auf den Grund zu kommen.

3. Die Ursache der A. sei auf rein psychologischer Basis zu suchen. Es würde zu weit führen, hier auf alle Theorien darüber einzugehen. *Stertz* hebt als Charakteristikum dieser Patienten eine erheblich gesteigerte Autosuggestibilität hervor und sieht, ebenso wie andere, die Erklärung der Frage in der Ähnlichkeit zwischen der A. und gewissen »hysterischen Mechanismen«. Alle die verschiedenen Deutungen ergeben sich aus der psychologischen Schule, zu der sich der jeweilige Artikelverfasser bekennt. Handelt es sich um das psychische Erleben eines

Menschen mit seinem von Fall zu Fall verschiedenen Charakter, so scheint mir zweifellos nur eine Erklärung, die auf einer Individualpsychologie aufbaut, zum Ziele führen zu können.

Eine Deutung des verwandten Antonschen Syndromes (in der ursprünglichen Form »ein Zustand mangelhafter Einsicht eigener Blindheit und Taubheit«) wurde 1941 von *Lunn* versucht. Diese Deutung, die auch die A. umfassen zu können scheint, was im übrigen *Lunn* selbst andeutet, baut auf der »struktur-analytischen« Lehre von *Birnbaum* auf, wie sie in seiner Arbeit »Der Aufbau der Psychose« dargelegt wird. Die grösste Bedeutung der Theorie von *Lunn* liegt meiner Ansicht nach darin, dass er das Konstitutionsproblem in die Diskussion einführt. Dadurch wird die ganze Frage auf einen sichereren Grund gestellt und gleichzeitig Licht über die schwer zu deutende Tatsache verbreitet, dass die A. nur bei bestimmten Personen einer grösseren Gruppe mit einem relativ gleichartigen somatischen Defekt vorkommt. *Lunn* formuliert seinen Schluss folgendermassen: »Das A.-Phänomen ist nicht in dem Sinne unteilbar, dass es als psychisches Äquivalent eines lokalen anatomischen Defektes allein auftritt, sondern es muss im Gegenteil als die Resultante eines Zusammenwirkens verschiedener Elemente angesehen werden«.

Wie oben erwähnt, hielt ich es für angebracht, in die Definition des A.-Begriffes den Begriff des Erlebens einzuführen. Nach *Sjöbring* ist das bewusste Erleben nichts anderes als ein Ausdruck für den realen Prozess, den wir uns als spezifischen energetischen Hirnprozess denken. »Wenn wir keinen Zusammenhang zwischen der Tätigkeit bestimmter Gewebelemente und bestimmter Erlebnisse annähmen, wären wir gezwungen, jeden Versuch, die Veränderungen unserer Erlebnisse als mit einem veränderten Funktionszustand der einzelnen Gewebelemente kausal zu erklären, aufzugeben, d. h. wir müssten den Gedanken aufgeben, unsere Erlebnisse in einen Zusammenhang mit Veränderungen der materiellen Wirklichkeit zu bringen« (*Kinberg*).

Hier handelt es sich darum, sich ein Urteil über das Erleben des Kranken zu bilden. Ein Mensch — gesund oder krank —

drückt durch seine Sprache und Mimik aus, was er erlebt. Auf diese Weise bringt er seine psychische Tätigkeit zum Ausdruck. Die Reaktionen anderer Menschen erleben wir in Form von etwas Selbsterlebtem. Jedes Individuum erlebt auf seine eigene Weise, die sich von der der anderen unterscheidet.

Wir wissen, dass unsere psychische Tätigkeit unter verschiedenen Umständen nicht gleich ist. Wir nehmen an, dass im wachen Zustand in unserem Gehirn zahlreiche Prozesse ablaufen; während des Schlafes ist deren Anzahl jedoch reduziert. Bei Zuständen mit einem herabgesetzten Grad des Wachseins ist, wie man sagt, das Tätigkeitsfeld freier, und hierdurch können die durch die ankommenden Reize ausgelösten Prozesse einen freieren Verlauf gewinnen. Das Erleben dieser Vorgänge bekommt oft den Charakter dessen, was wir als Wahnvorstellungen zu bezeichnen pflegen (z. B. hypnagogische Halluzinationen). Die A. ist eine Wahnvorstellung. Ihre Entstehung kann durch die stärkere oder schwächere »Beeinflussung des Sensoriums«, die nach den Krankengeschichten dieser Patienten ein konstanter Befund ist, erklärt werden. Sind also die Bedingungen für das Zustandekommen der Wahnvorstellung vorhanden, so erhebt sich die Frage, worin der Mechanismus dieser Wahnvorstellung im konkreten Fall besteht.

Ich gehe davon aus, dass der Kranke erlebt, er bewege seinen lahmen Arm. Dies bedeutet, dass ein Reiz einen Prozess in dem Feld in Gang gesetzt hat, und dies wird von dem Patienten so erlebt, als ob er seinen Arm bewege. Da der Arm tatsächlich gelähmt ist, kann ein derartiger Prozess durch keinen durch die Bewegung des Armes verursachten zentripetalen Reiz ausgelöst werden. Können wir uns nun vorstellen, dass andere Prozesse beim Kranken das Erleben einer Armbewegung erzeugen? Meiner Ansicht nach ist das möglich. Es ist z. B. kein äusserer Reiz notwendig, um eine bestimmte Person erleben zu können. Wir haben die Fähigkeit, sie uns zu denken, uns vorzustellen. Wir können sehr gut erleben, dass wir unseren Arm heben, trotzdem wir ihn nicht bewegen. Wir können in der Tat auf diese Weise sehr komplizierte Armbewegungen erleben. Um dies mit grösserer Intensität erleben zu können, müssen wir

die übrigen Prozesse so weit wie möglich ausschalten, d. h. uns ganz darauf einstellen. Das Geringste, was »zerstreut« — d. h. andere gleichzeitige Prozesse starker Aktualität — lässt dieses Erleben weniger deutlich werden. Bei Zuständen, in denen der Grad des Wachseins herabgesetzt ist, laufen weniger Prozesse ab, und die Bedingungen sind — wie oben erwähnt — dafür vorhanden, dass dieses Erleben für uns stärker und anschaulicher, wie im Traum wird.

Die Fähigkeit, Vorstellungen lebendig zu machen, ist jedoch bei den einzelnen Individuen sehr verschieden. Sogar bei ein und demselben Individuum ist sie von verschiedenen äusseren Bedingungen abhängig. Die psychische Tätigkeit des Menschen wird im wesentlichen durch zwei verschiedene Faktoren bedingt, durch die psychische Konstitution und durch das, was wir mit einem Wort als Milieu bezeichnen können. Will man das Erleben verschiedener Menschen untersuchen, so kann man den einen Faktor, nämlich das Milieu, konstant machen. (Theoretisch möglich bei jedem Fall). Der andere Faktor, die psychische Konstitution, ist dagegen bei jeder Person anders. Daraus folgt, dass die psychische Tätigkeit unter gleichartigen Milieubedingungen durch die psychische Konstitution bestimmt wird, und hieraus geht hervor, dass das Untersuchungsergebnis des konkreten Falles nicht befriedigend sein kann, wenn man nur die Milieufaktoren, in diesem Fall die Schädigung, berücksichtigt. Nur eine kombinierte Untersuchung dieser und der psychischen Konstitution des Kranken — seines »psychischen Status« vor der Erkrankung — kann schlussfähige Resultate ergeben. Hierin scheint mir die Ursache dafür zu liegen, warum nur wenige Hemiplegiker das Symptom der A. aufweisen. Es mag erwähnt werden, dass mehrere Kranke mit dem damit verwandten Antonschen Syndrom Taboparalytiker waren, also eine Verstimmung hatten. Alle blinden Taboparalytiker zeigen jedoch nicht das Antonsche Syndrom. Auch hier ist offenbar ein konstitutioneller Faktor vorhanden.

Obwohl auf einem anderen Wege als *Lunn*, scheine ich also in dieser Frage zu demselben Schluss zu kommen wie er, dass nämlich die Ursache nicht »unteilbar«, sondern als die »Re-

sultante einer Zusammenwirkung verschiedener Elemente« anzusehen ist. Ich glaube, dass es für die Erforschung der Genese der A. bedeutungsvoll sein wird, wenn man den von mir oben angedeuteten Weg weiter verfolgt.

Zu untersuchen ist noch ein Problem. Warum sind die meisten Fälle linksseitig? Wahrscheinlich ist die Ursache dafür die von *Barkman* vermutete, die ich oben referiert habe. Seine Annahme muss jedoch auf Grund unserer jetzigen Kenntnisse modifiziert werden. Vielleicht ist der Grund darin zu suchen, dass die meisten Patienten mit rechtsseitiger Hemiplegie und so hochgradiger Schädigung, dass eine A. auftritt, auch eine so starke Aphasie haben, dass man mit ihnen nicht in genügenden Kontakt kommen kann, um feststellen, ob sie anosognostisch sind.

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FURTHER STUDIES ON THE BIOCHEMISTRY OF EPILEPSY¹

BY

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¹ Translated from Danish by Hans Andersen, M.D.

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I. INTRODUCTION

The more recent biochemical research in epilepsy has dealt in particular with studies on the acid-base balance and studies on the water-salt metabolism.

In 1918 Bisgaard, Jarløv & Nørvig reported the result of some preliminary studies on the neutrality regulation in epilepsy, in which they demonstrated certain abnormalities in the pH of the blood, pH of the urine, and ammonia content of the urine. These studies gave rise to a number of works on the acid-base balance in epilepsy. Jarløv has investigated thoroughly the acidity of the blood in epileptics and found an increase in the reduced pH of the blood in the preparoxysmal period, together with a low reduced pH in the postparoxysmal period. These findings of Jarløv have subsequently been confirmed essentially by other investigators (Geyelin, Bigwood, Frisch & Fried; Dautrebande and others). The cited investigations were carried out either after Hasselbalch's indirect method (calculation of pH after determination of the free and combined CO₂ tension) or on serum, mostly after Cullen's colorimetrical method. In recent years, determinations of pH have been made on whole blood by employment of the glass electrode, among others by Faurbye¹ who found similar abnormalities as reported by earlier investigators. In epileptics, as a rule, the pH of the blood falls within the normal limit, though with a somewhat greater range of variations, especially in alkaline direction, and usually the values for pH are high in the paroxysmal period.

At the same time as Jarløv carried out his studies on the

¹ In further investigations on the same subject Faurbye recently did not find any sure abnormalities in serum —pH on epileptics.

pH of the blood, Bisgaard & Nørvig continued their investigations on the urine and demonstrated that the regular relation between the pH of the urine and its ammonia content given by Hasselbalch is not found in epileptics (ammoniac dysregulation).

Subsequent investigations have shown that the conditions are more complicated than assumed at first (*e.g.*, Larsen, Schrøder, Bigwood, Eriksen, Levinsen & Warburg, Stubbe Teglbjærg & Madsen, Gozzano, Madsen) and nearly all have confirmed that the relation between the urinary pH and the ammonia output in epileptics is abnormal, as on an average pH is higher and the ammonia output greater than normally. Madsen lays particular stress on the increased ammonia output as the abnormality which is most easy to recognize (hyperammoniuria).

In recent years the biochemical research in epilepsy has been stamped in particular by studies on the water and salt metabolism. Even the older epilepsy literature brought some observations on disturbances in the water excretion in epilepsy (Féré, Hallager, Allers, Rohde), but it is particularly the works by McQuarrie and collaborators that have again called attention to these studies, showing that a diet rich in water causes more epileptic seizures than a low water diet. Stubbe Teglbjærg was able in a large epileptic material to confirm the observations of McQuarrie. On the other hand, Stubbe Teglbjærg was able to demonstrate that the water retention in epileptics is not particularly great when the patients prior to the experiments are adjusted thoroughly to a water and salt balance, and when the water intake during the experiments is watched closely. So the connection between the water and salt metabolism and the epileptic seizures still remains an open question.

In a work of 1933 Jørgen Madsen asserted that it is reasonable to assume a relation between hyperammoniuria and the disturbances in the water-salt metabolism ascertained by other investigators. It is rather likely that in epileptics the tissues periodically are capable of an abnormally firm combination with water and salts, especially the solid alkalies. As the strong acids of the organism cannot be excreted as free acids but have to be

excreted in combination with alkali metals or as ammonium salts, it seems obvious that the periodically difficult mobilization of solid alkalies must bring about an increased ammonia output. For the present this view has to be looked upon as a hypothesis, but to me it seems that it will be of considerable importance if this view can be demonstrated to hold true, as then it is likely to afford some valuable information about the essential in the various abnormalities found in epileptics. The above-mentioned studies on the biochemistry of epilepsy are encumbered with a fact of uncertainty, however, as similar studies have not been carried out to a sufficient extent on patients suffering from other medical, especially neurologic-psychiatric, affections, and hence it cannot be taken for granted that the reported disturbances are characteristic of epileptics. Several observations suggest that this is not the case.

It is a well-known thing that various other affections—for instance, lesions of endocrine nature—are associated with the disturbances in the water and salt exchange, and studies on the occurrence of hyperammoniuria have shown that this phenomenon is not so specifically connected with the so-called genuine epilepsy that was assumed originally. It is encountered also in patients with convulsions of exogenous nature, and further occasionally in apparently widely different neuropsychiatric affections, *e.g.*, not infrequently in typical schizophrenia. This fact detracts from the immediate practical significance of these investigations, which in return open a wider perspective, for instance, as hyperammoniuria then cannot be interpreted as an entirely concomitant phenomenon in convulsive patients but has to be looked upon as a part in an anomaly of metabolism frequently present in various affections of the central nervous system. It is only natural, I think, to look for the real cause of these disturbances either in a dysfunction of certain regulatory brain centers—centers in the hypothalamus suggest themselves especially—or in hormonal disturbances; in either case, the problem is highly interesting.

When these disturbances are found so often in epileptics, it probably is because they form a fairly good soil for the de-

velopment of epileptic convulsions, so that together with other epileptogenic factors (*e.g.*, injury to the brain) they bring about the development of epilepsy.

It seems to me that a continuation of these studies primarily should consist in a more thorough analysis of the various abnormalities. In the work here presented I have tried to analyze the nature and cause of hyperammoniuria, in particular its relation to the water-salt exchange. The following questions have been investigated:

1. Are disturbances of the water-salt metabolism present in patients with hyperammoniuria?
2. If so, is there any demonstrable causal connection between such disturbances and the hyperammoniuria?
3. What is the cause of these disturbances?

II. STUDIES ON THE WATER AND SALT METABOLISM IN EPILEPSY

Studies on the water and salt metabolism naturally include examination of the conditions in the blood as well as the aspects of excretion. The most reliable way for the solution of the problem will be systematic simultaneous determination of the water exchange and the electrolyte content of the blood and excretions. This task will be impracticable outside the special laboratories, however, and the investigators who have carried on this kind of studies have therefore limited the task and dealt merely with various aspects of the problem. But the information obtained in this way about the total water and salt metabolism is incomplete; in particular even when a series of such examinations give a negative result, it is not warrantable to conclude that the water and salt metabolism on the whole is normal.

Thus, when Stubbe Teglbjærg finds that epileptics have fewer seizures in periods of lower water intake than in periods of great water intake, while it is not possible through careful water balance tests to ascertain any periodical water retention to speak of, two things may be concluded from his findings, namely: In the first instance, that the water exchange may play some

rôle in the pathogenesis of the convulsions; in the next place, that in these patients no shift takes place in the total water content of the organism that can be ascertained with the method employed. On the other hand, the experiments tell us nothing, for instance about possible shifts in the water content within the various tissue elements of the organism. Further, his experiments give information only about the state of the patients under the experimental conditions employed by him, with close watch on the water and salt intake. From the absence of water retention under limited water supply, the possibility cannot be excluded that the patient might retain the water if he had a chance to take water *ad libitum*.

This illustrates the delicacy of the experiments here concerned. On the one hand, it is necessary to encompass the problems by a suitable experimental plan; but, on the other hand, it is essential constantly to be aware of the possibility that the interference with the physiological conditions implied by the experimental plan may have some influence on the results and give rise to misinterpretations.

Thus it appears to me that Stubbe Teglbjærg's findings do not conclusively disprove the results obtained by other investigators that have been suggestive of pathological conditions in the water and salt metabolism of epileptics. The problems are as yet so far from being elucidated that it is not possible to survey the conditions comprehensively, and to me it seems more expedient for the present to encompass the problems by investigating a number of questions within this subject in relatively short experimental series. In this way, I think, it will be practicable to gather a material that gives better information about the water and salt metabolism in general than may be obtained through extensive studies within a limited field.

It is this technique I have employed in the present work. I have tried to elucidate the problem from various sides and then correlate the various observations. In this way it could not be helped that individual experimental series are so short that, taken individually, they furnish no conclusive evidence. But I trust that this shortcoming of the various experimental is counterbalanced by their correlation.

A. STUDIES ON THE ELECTROLYTE CONTENT OF THE BLOOD IN PATIENTS WITH NORMO- AND HYPERAMMONIURIA

A number of works have been published on the electrolytes of the blood in epileptics without resulting in reliable and uniform data. Several investigators think they have been able to ascertain the presence of minor abnormalities, but these have usually been very slight and inconstant; besides, the findings obtained by the various investigators concerning the behavior of the same electrolytes have not been quite concordant.

The electrolytes most often investigated are Ca, Na, and Cl. At first, interest was taken particularly in the Ca ion on account of its antispasmodic effect against tetanic phenomena and the supposed connection between epilepsy and tetany. It was found, however, that the very low Ca values observed in tetany are not encountered in epileptics, and various investigations have shown that there is not likely to be any intimate connection between the two lesions (Hendriksen).

Most studies concerning Ca in epilepsy have merely been aimed at determination of the total Ca, however, although probably only a part of this total calcium is ionized or active. For this reason some authors (*e.g.*, Bigwood) have claimed that although the values for total Ca in epileptics are normal it is possible that the amount of active Ca ions may be lowered. The ionization would be dependent on the pH of the blood, they assert, so that an increased pH means a decreased amount of total Ca in active form. According to the present studies, however, the variations of pH are slight, and as epileptics otherwise show no symptoms of Ca deficiency, it is hardly probable that calcium might play any essential rôle in the pathogenesis of epilepsy.

In recent years attention has been paid particularly to the Na and Cl ions, because the water and salt exchange has come to the foreground in biochemical research in epilepsy. Ordinary serial analyses of the Na and Cl contents of the blood have shown no conspicuous and constant abnormalities. In a previous work I have investigated the Ca, Na and K contents of the serum in epileptics, and for comparison a corresponding number

of control patients were examined. All three electrolytes were found to show a tendency to low values, but the obtained values were rather seldom under the lower normal limits, and no particular changes were found in connection with the seizures.

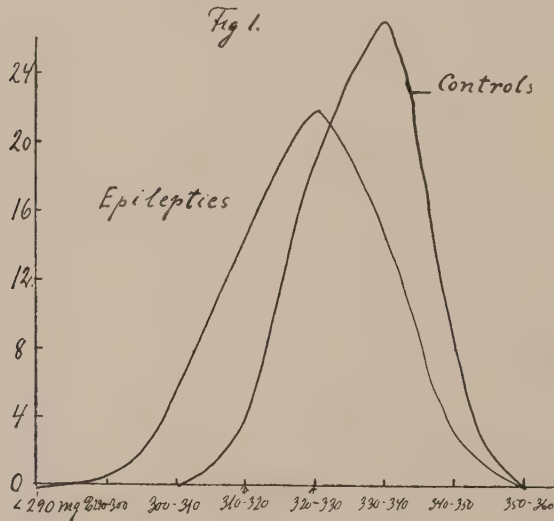
As to Na, the values here obtained were distributed as follows:

	280— 290	290— 300	300— 310	310— 320	320— 330	330— 340	340— 350
Control patients	0	0	0	4	19	27	7
Epileptics	0	1	5	15	22	15	3

Even though most of the values fall within the normal range of variations, from 320 to 350 mg.%, there is still a distinct tendency for low values (see Fig. 1).

Nor does the Cl content of the serum show any particular changes in epilepsy (Lennox & Allen).

But, even though the abnormalities in the occurrence of the



Distribution curves for the Na content of the serum in epileptics and control patients. The epileptic curve shows a wider dispersion of the values, with a tendency to low values, as compared to the curve for the controls. In the controls the majority of the values fall between 330 and 340 mg.%, in the epileptics between 320 and 330 mg.%.

electrolytes in the serum of epileptics are slight, they cannot a priori be considered insignificant, especially when we keep in mind that the amount of these substances in the blood under normal conditions is extraordinarily constant. This applies especially to Na. In 57 determinations on 20 normal subjects I found serum Na to fall between 319 and 340 mg.% (Kramer-Gittelman's modified method). Other authors, too, employing serviceable methods (titrimetric) have found a great constancy in human blood and shown that it is difficult to produce any marked changes in the Na concentration of the blood even by intravenous injection of NaCl. Further, Warburg & Christensen have shown that even a protracted Russian bath does not produce any great change in the osmotic aspects of the blood.

So in this respect the electrolytes of the blood are subject to a very precise regulation. When the sodium supply of the blood is increased, a corresponding amount of Na is given off by the blood to the tissues or excreted with the urine, so that the Na concentration of the serum is kept constant. When this is the case, however, it is not to be expected that even considerable abnormalities in the salt metabolism of the organism would give great demonstrable changes in the blood. On the other hand, it is reasonable to expect that the blood will reflect a tendency to high or low values when pathological changes occur in the accumulation of electrolytes in the tissues or when the excretion is abnormal.

As a supplement to previous studies on spontaneous variations of the electrolytes in epileptics, therefore, I have tried in various ways to influence the sodium concentration of the blood—by intravenous injection of NaCl and by administration of diuretics and antidiuretics—besides looking into this matter under hyperventilation. In several of these examinations the Cl and Ca concentrations of the serum were determined at the same time. These studies were carried out in part on control subjects (paralytics), in part on epileptics with hyperammonia, as it seemed possible that such "tolerance tests" might disclose disturbances in the salt metabolism that are not manifest in the spontaneous variations.

The Na concentration is determined after Kramer-Gittelman's method with a few modifications (Jørgen Madsen), Ca after Kramer-Tisdall's method, and Cl after a method given by Gøthgen. The analyses were always carried out in duplicate.

a. *On the Influence of Intravenous Injection of NaCl upon the Na Content of the Serum.*

The experiments were made in the morning at 9 o'clock, on fasting stomach. The patients had not been placed on any particular diet prior to the experiments. The injections were given into the cubital vein of the left arm. The samples of blood were taken from another cubital vein—as a rule from the right arm,—but in some cases from the same arm as used for the injection. The needles, of a fairly large caliber were dry-sterilized. Immediately after the blood was taken, it was defibrinated by shaking with glass beads, and the serum was separated by centrifuging.

Experiment 1: Control patient.

At 10,42,00: Blood sample	323 mg.% Na
„ 10,44,40: Injection of 10 cc. of 25 % NaCl.	
„ 10,45,00: Injection concluded. Blood sample	323 mg.% Na
„ 10,45,50 to 10,46,10: Blood sample	339 mg.% Na
„ 10,46,10 to 10,48,00: Blood sample	324 mg.% Na

Experiment 2: Control patient.

At 9,29,50: Blood sample	314 mg.% Na	9.5 mg.% Ca
„ 9,31,30 to 9,32,00: Inj. of 10 cc. of 25 % NaCl.		
„ 9,32,00 to 9,32,30: Blood sample	313 mg.% Na	9.8 mg.% Ca
„ 9,32,30 to 9,33,00: „ „	323 mg.% Na	9.8 mg.% Ca
„ 9,33,00 to 9,34,15: „ „	315 mg.% Na	

Experiment 3: Control patient.

At 9,05,20 to 9,06,00: Blood sample	333 mg.% Na
„ 9,16,00 to 9,16,30: Inj. of 20 cc. of 25 % NaCl.	
„ 9,16,40 to 9,17,30: Blood sample	351 mg.% Na
„ 9,17,35 to 9,19,20: „ „	343 mg.% Na

Experiment 4: Control patient.

At 9,35,00: Blood sample	320 mg.% Na
„ 9,36,40 to 9,37,40: Inj. of 20 cc. of 25 % NaCl.	
„ 9,40,00 to 9,41,45: Blood sample	322 mg.% Na
„ 9,41,45 to 9,43,00: „ „	323 mg.% Na
„ 9,43,00 to 9,44,00: „ „	322 mg.% Na

Experiment 5: Epileptic.

At 9,14,20: Blood sample	323 mg.% Na	
„ 9,16,00: „ „	323 mg.% Na	9,2 mg.% Ca
„ 9,16,20 to 9,17,10: Inj. of 20 cc. of 25 % NaCl.		
„ 9,17,20 to 9,18,20: Blood sample	327 mg.% Na	10.0 mg.% Ca
„ 9,18,30 to 9,19,00: „ „	316 mg.% Na	9.2 mg.% Ca
„ 9,22,00 to 9,26,00: „ „	320 mg.% Na	
„ 9,34,30 to 9,35,30: „ „	321 mg.% Na	10.0 mg.% Ca

Experiment 6: Epileptic.

At 9,30,00: Blood sample	332 mg.% Na	11.6 mg.% Ca
„ 9,31,00 to 9,31,40: Inj. of 20 cc. of 25 % NaCl.		
„ 9,32,15 to 9,32,45: Blood sample	334 mg.% Na	9.8 mg.% Ca
„ 9,32,45 to 9,33,25: „ „	328 mg.% Na	10.6 mg.% Ca
„ 9,33,25 to 9,34,20: „ „	335 mg.% Na	10.2 mg.% Ca
„ 9,34,20 to 9,35,00: „ „	332 mg.% Na	10.0 mg.% Ca

Experiment 7: Epileptic.

At 9,30,00: Blood sample	336 mg.% Na
„ 9,31,10 to 9,31,50: Inj. of 20 cc. of 25 % NaCl.	
„ 9,32,40 to 9,33,40: Blood sample	346 mg.% Na
„ 9,33,40 to 9,36,50: „ „	340 mg.% Na

Thus the experiments show that intravenous injection of from 10 to 20 cc. of 25 % NaCl solution in the controls is followed by a minimal rise in the sodium concentration of the serum 1-2 min. after the injection. This increase is of very brief duration, and after 3 min. the Na concentration is the same as before the injection. The increase amounts respectively to 16, 10 and 18 mg.%. In Exp. 4, with an interval of 2-3 min. between the conclusion of the injection and the first blood sample, the analysis shows no increase in blood Na. The increases observed in these experiments are of such magnitude that at any rate

those of the first two experiments fall outside the standard deviation of the method (10 mg. %).

From the experiments with injection of 20 cc. of 25 % NaCl it would be reasonable, however, to expect an increase of more than 50 mg.% if the injected amount of sodium were distributed evenly in the circulating blood; and there can be no doubt that the greater part of the injected Na leaves the blood stream at once, presumably being taken up from the tissues or excreted from the kidneys. Still, the possibility has to be considered that Na remains in the blood stream, withdrawing water from the tissues to the blood stream so that the concentration remains constant. If so, there would be a constant fall in the Ca concentration—and this is not the case. More likely the excess of Na enters into the tissues, as it cannot be excreted so rapidly by way of the kidneys. In order to throw some light on this question I have determined the Na output through the kidneys during the first 5-6 hours after the injection—as illustrated by the following experiment:

Na Output in the Urine after Injection of 20 cc. of 25 % NaCl Solution.

1 hour before exp. : Diuresis 24 cc., with 440 mg.% Na.										Output : 105 mg. Na				
1	“	after	“	“	62	“	“	437	“	“	“	271	“	“
2	hours	“	“	“	54	“	“	437	“	“	“	236	“	“
3	“	“	“	“	65	“	“	447	“	“	“	290	“	“
4	“	“	“	“	70	“	“	551	“	“	“	385	“	“
5	“	“	“	“	80	“	“	445	“	“	“	358	“	“
6	“	“	“	“	64	“	“	448	“	“	“	287	“	“

Thus there is an increased output of Na for several hours after the injection, reaching its maximum in 4 hours. Even though this increase in the output will be ascribable to the injection—which can by no means be taken for granted—it can be explained only in this way, that the injected amount of Na is first given off to the tissues and later returned again to the blood stream, together with a corresponding amount of water, and then excreted through the kidneys. In the 6 hours the total output of Na is 0.8 g., that is, less than the injected amount (about 2 g.).

The epileptics showed even a smaller effect on the Na content

of the serum from the injections, as no real increase could be demonstrated in any of the experiments, the variations falling within the limit of experimental error for the method.

None of the examined epileptics had convulsive seizures or other epileptic phenomena in connection with these experiments.

b. *On the Influence of Diuretics upon the Na and Cl Concentrations of the Blood.*

The diuretics employed were salyrgan, which was injected intravenously, and theophyllin, which was given by mouth. In the salyrgan experiments the patients were not beforehand adjusted to salt equilibrium, but the experiments were performed in the morning on fasting stomach, and the patients had nothing to eat or drink during the experiments. In the theophyllin experiments the patients were given a preliminary diet of the following composition:

Morning: 1 g. NaCl and salt-free bread and butter + tea.

Breakfast: 250 g. oatmeal gruel and 250 g. milk.

Dinner: 2 g. NaCl and 1 egg, salt-free bread and butter, and 250 g. oatmeal gruel.

Afternoon: 200 g. cream.

Supper: 2 g. NaCl and 1 egg, salt-free bread and butter, 250 g. milk, and tea ad libitum.

This diet was given for 2 days prior to the experiments. On the experimental day the patients had nothing to eat or drink before the experiment was concluded.

Theophyllin was given at a dosage of 8 mg. per kg. of body weight.

Salyrgan Experiments.

At 8 o'clock 2 cc. of salyrgan was injected intravenously. A sample of blood was taken immediately before.

Experiment 1. Epileptic.

Before injection	310 mg.% Na	365 mg.% Cl
30 min. after injection	322 " "	380 " "
1 hour " "	316 " "	390 " "
3 hours " "	314 " "	377 " "

Experiment 2. Epileptic.

Before injection	311 mg.% Na	356 mg.% Cl
15 min. after injection	313 " "	368 " "
30 " " "	316 " "	366 " "
1 hour " " "	313 " "	371 " "

Experiment 3. Epileptic.

Before injection	331 " "	375 " "
15 min. after injection	289 " "	360 " "

The first two experiments show an insignificant rise in the Na concentration of the blood and a slightly higher rise in the Cl concentration. The third experiment shows a marked fall in the Na concentration and a slight fall in the Cl concentration. Prior to the injection the last patient had a severe epileptic seizure; but no convulsions appeared immediately after the experiment.

*Theophyllin Experiments.**Experiment 1. Control patient.*

Before the experiment	(analysis failed)	
45 min. after theophyllin	293 mg.% Na	350 mg.% Cl
1½ hours " " "	300 " "	346 " "

Experiment 2. Control patient.

Before the experiment	330 mg.% Na	404 mg.% Cl
1 hour after theophyllin	328 " "	383 " "
2½ hours " " "	320 " "	353 " "
3 " " " "	328 " "	368 " "

Experiment 3. Control patient.

Before the experiment	(analysis failed)	
15 min. after theophyllin	328 mg.% Na	395 mg.% Cl
1 hour " " "	315 " "	381 " "

Experiment 4. Epileptic.

Before the experiment	323 " "	" "
1¼ hours after theophyllin	321 " "	" "
2¼ " " " "	325 " "	" "
3 " " " "	315 " "	" "

Experiment 5. Epileptic.

Before the experiment	(analysis failed)
15 min. after theophyllin	338 mg.% Na
30 " " " "	322 " "
1 hour " " "	314 " "
2 hours " " "	320 " "
3 " " " "	323 " "

Experiment 6. Epileptic.

Before the experiment	(analysis failed)
30 min. after theophyllin	331 mg.% Na 388 mg.% Cl
2 hours " " "	327 " " 379 " "

Experiment 7. Epileptic.

Before the experiment	301 mg.% Na
30 min. after theophyllin	308 " "
45 " " " "	321 " "
2½ hours " " "	320 " "
3 " " " "	315 " "
4½ " " " "	302 " "

Experiment 8. Epileptic.

Before the experiment	316 mg.% Na
45 min. after theophyllin	314 " "
1½ hours " " "	317 " "
3 " " " "	315 " "

Experiment 9. Epileptic.

Before the experiment	323 mg.% Na
30 min. after theophyllin	330 " "
1¾ hours " " "	324 " "
2½ " " " "	309 " "
3 " " " "	322 " "

Experiment 10. Epileptic.

Before the experiment	321 mg.% Na
30 min. after theophyllin	312 " "
1 hour " " "	312 " "
1½ hours " " "	321 " "
2 " " " "	323 " "

Experiment 11. Epileptic.

Before the experiment	327 mg.% Na	
1 hour after theophyllin	323	" "
2½ hours " "	324	" "
3½ " " " "	322	" "

Experiment 12. Epileptic.

Before ¹ the experiment	314 mg.% Na	372 mg.% Cl
30 min. after theophyllin	299	" " 370 " "
1 hour " "	297	" " 357 " "
2 hours " "	300	" " 362 " "
3 " " " "	335	" " 366 " "
4 " " " "	326	" " 372 " "

At 12 o'clock (noon) the patient had a severe epileptic seizure and in the following hour he had 4 additional attacks.

Experiment 13. Epileptic.

Before the experiment	(analysis failed)	
At 8,30	272 mg.% Na	426 mg.% Cl
" 9,15	240	" " 342 " "
" 9,55 epileptic seizure		
" 11	345	" " 376 " "

Experiment 14. Epileptic.

Before the experiment	333 mg.% Na	394 mg.% Cl
At 9	306	" " 365 " "
" 10	279	" " 371 " "
" 13 epileptic seizure.		

Experiment 15. Epileptic.

Before the experiment	313 mg.% Na	409 mg.% Cl
At 9	276	" " 361 " "
" 14 epileptic seizure.		

In the theophyllin experiments thus nearly all the patients showed a greater or smaller fall in the Na and Cl concentrations, with the following minimum values:

¹ In all the experiments theophyllin was given at 8 a. m.

						<i>Minimum values.</i>		
Pt. No. 1.	Control patient					293 mg.% Na	346 mg.% Cl	
" "	2.	" "				320	" "	353
" "	3.	" "				315	" "	381
" "	4.	Epileptic in convulsion-free phase				315	" "	
" "	5.	" "	" "	" "	" "	314	" "	
" "	6.	" "	" "	" "	" "	327	" "	
" "	7.	" "	" "	" "	" "	302	" "	
" "	8.	" "	" "	" "	" "	314	" "	
" "	9.	" "	" "	" "	" "	309	" "	
" "	10.	" "	" "	" "	" "	312	" "	
" "	11.	" "	" "	" "	" "	322	" "	
" "	12.	" "	convulsive phase	...		297	" "	357
" "	13.	" "	" "	" "	...	240	" "	342
" "	14.	" "	" "	" "	...	279	" "	365
" "	15.	" "	" "	" "	...	276	" "	361

These findings concerning the Na concentration in the blood after administration of theophyllin are presented graphically in Fig. 2.

The findings thus are the same in the control patients and in epileptics in a convulsion-free phase, with a moderate fall in the Na and Cl concentrations, but the serum Na does not fall below a level of about 300 mg.%, Cl not below 350 mg.%. There is no absolute parallelism between the Na and Cl concentrations, indicating that it is not a question of simple dilution of the blood. Four of the epileptics had convulsive seizures during, or immediately after, the experiments, and they all showed a considerably greater fall in serum Na and Cl. This fall is greatest in Exp. 13, in which the patient had an attack in the middle of the experiment. Forty minutes before the seizure the Na concentration is extraordinarily low (240 mg.%); after the seizure it is 340 mg.%—that is, a variation of about 100 mg.%. Half-an-hour after the intake of theophyllin the Cl concentration is found to be increased (426 mg.%), and in the following hour it falls off to 342 mg.%, that is, a fall of 80 mg.%. Similar features, though less pronounced, are seen in the other epileptics in the convulsive phase. There is no difference in the fasting serum Na—*i.e.*, before the experiments—in the patients who

have seizures and those who have no seizures. On the other hand, patients in the convulsive phase show a tendency to increased Cl values prior to the experiments, so that these values do not reach a pathological level, in spite of their great fall.

In Exp. 12, in which the patient had a series of seizures 4 hours after the intake of theophyllin, both the Na and the Cl

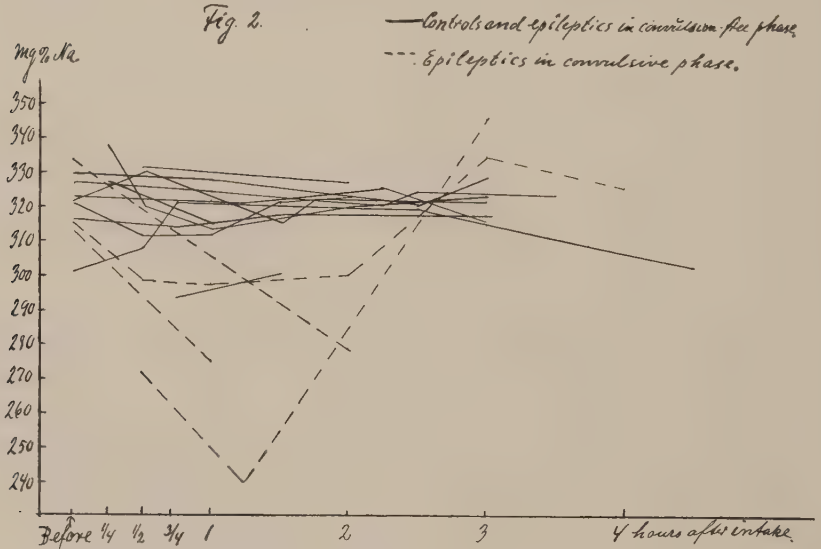


Fig. 2.

Variations in the Na concentration of serum after intake of theophyllin. In the control patients and the epileptics in a convulsion-free phase, the Na concentration is either constant or falls but slightly. In epileptics in the convulsive phase there is a considerable fall in the Na concentration in the first hours after intake of theophyllin, followed by a rise to the initial level and even higher.

concentrations are seen to fall during the first hour and then rise to normal level prior to the convulsive attacks, showing that there is no direct connection between the electrolyte content of the serum and the seizures. So, if there be any connection between the effect of theophyllin on the electrolytes and the convulsive attacks, we shall have to assume that they both are coordinate results of the same cause—for instance, abnormalities in the colloid-osmotic aspects of the cells.

In connection with the theophyllin experiments, it will be appropriate to look upon the third salyrgan experiment, where the patient had an epileptic seizure prior to the experiment. Here, too, we find a considerable fall in the Na concentration (from 331 to 298 mg.%), whereas there is only a slight fall in the Cl concentration (from 375 to 360 mg.%). It seems, then, as if the abnormal effect of diuretics not only appears prepa-roxysmally but also persists postparoxysmally.

These experiments show, then, that administration of diuretics in epileptics in a convulsive period is able to produce a considerable fall in the Na and Cl concentrations of the serum, whereas this is not the case in approximately the same degree in control subjects or in epileptics in a convulsion-free period. These experiments are only few in number, but it is very difficult to collect any large material if the patients are to receive a preliminary diet for some days in order to bring them into a state of water and salt balance, as it will be a matter of chance whether the patients then have a seizure on the experimental day in immediate connection with the experiment. The phenomenon recorded in the present experiments is so constant that it can hardly be due to accidental factors.

c. *Effect of Pitressin Injection on the Na and Cl Concentrations of the Serum.*

Experiment 1. Epileptic.

Before injection	302 mg.% Na	379 mg.% Cl
1 hour after injection	326 " "	364 " "

Experiment 2. Epileptic.

Before injection	321 mg.% Na	344 mg.% Cl
15 min. after injection	325 " "	330 " "
1 hour " "	319 " "	337 " "

The patients were given 1 cc. of pitressin subcutaneously, as this dose was thus unable to produce any sure variation in the Na and Cl concentrations. Neither patient had any seizure in connection with the experiment.

d. *Effect of Hyperventilation on the Na and Cl Contents of the Serum.*

In addition I have looked into the effect of hyperventilation on the electrolyte Na, Cl and Ca, as it will be of interest to learn whether this convulsion-eliciting procedure produces any change in the electrolytes. This seemed the more important, as one of the explanations offered for the tetany- and convulsion-provoking effect of hyperventilation has been that, in order to compensate for the CO₂ loss under hyperventilation, there is an increased transport of Na from the blood to the tissues, making a shift in the proportion between Na and Ca in the tissues in favor of Na (Grant & Goldman, Collip & Bachus).

<i>Exp. 1. Epileptic.</i>	Before hyperventilation:	338 mg.% Na	378 mg.% Cl
	During	323 " "	381 " "
<i>Exp. 2. Epileptic.</i>	Before	322 " "	387 " "
	During	318 " "	368 " "
<i>Exp. 3. Epileptic.</i>	Before	330 " "	368 " "
	During	322 " "	372 " "
<i>Exp. 4. Epileptic.</i>	Before	326 " "	10.6 mg.% Ca
	During	322 " "	10.6 " "
	During	324 " "	10.5 " "
	"	323 " "	10.8 " "

An epileptic equivalent during the hyperventilation.

<i>Exp. 5. Epileptic.</i>	Before hyperventilation:	320 mg.% Na	10.1 mg.% Ca
	During	320 " "	11.2 " "
<i>Exp. 6. Epileptic.</i>	Before	324 " "	9.0 " "
	During	328 " "	9.3 " "

An absence during the hyperventilation.

<i>Exp. 7. Epileptic.</i>	Before hyperventilation:	324 " "	10.4 " "
	During	323 " "	11.2 " "
<i>Exp. 8. Epileptic.</i>	Before	318 " "	11.0 " "
	During	314 " "	11.2 " "
<i>Exp. 9. Epileptic.</i>	Before	320 " "	10.3 " "
	During	324 " "	10.6 " "

An absence during the hyperventilation.

<i>Exp. 10. Epileptic.</i>	Before hyperventilation:	322 mg.% Na	10.4 mg.% Ca
	During	324 " "	11.0 " "
<i>Exp. 11. Epileptic.</i>	Before	320 " "	
	During	329 " "	
<i>Exp. 12. Dem. paralyt.</i>	Before	339 " "	10.7 " "
	During	338 " "	11.2 " "
<i>Exp. 13. Dem. paralyt.</i>	Before	323 " "	10.6 " "
	During	333 " "	10.8 " "

These experiments show that hyperventilation produces no essential shift in the Na, Cl and Ca contents of the serum.

The present studies on the electrolytic aspects of serum show that the Na and Cl concentration of the serum are very constant and may be changed only with difficulty—for instance by injection of NaCl, diuretics or antidiuretics. Only in epileptics in the convulsive phase does administration of diuretics give a considerable fall in the Na and Cl concentrations. These investigations further show that possible changes in the water and salt exchange of epileptics cannot be expected to be reflected in the Na and Cl concentrations of the serum as massive changes. Hence the previous demonstration of only slight abnormalities in these electrolytic contents of the blood in epileptics by no means exclude the presence of significant abnormalities in the water and salt metabolism of epileptics. The experiments illustrate plainly that one-sided studies on blood chemistry cannot solve these problems, and that the investigations have to cover also the various aspects of the excretion.

B. STUDIES ON THE WATER AND SALT EXCRETION IN PATIENTS WITH NORMO- AND HYPERAMMONIURIA

a. *Diuresis and Na Output after Water Intake in Patients with Normo- and Hyperammoniuria.*

As mentioned already, the purpose of the present work was to investigate whether there be any connection between hyper-

ammoniuria and abnormalities in the water and salt metabolism. The studies on the electrolytic contents of the blood in epileptics with hyperammoniuria have on some points lent support to the assumption of previous authors concerning disturbances in the water and salt metabolism in epilepsy, but they have also shown that a demonstration of such disturbances is more likely to turn out positive successful in studies on various aspects of the excretion than in examination of the electrolytic content of the blood.

As the first step in the study of the excretion I have examined the water and sodium output after intake of 1 liter of water (Strauss' test).

It is generally recognized that the performance of such examinations requires a preceding adjustment of the organism to a water and salt equilibrium if the results are to be reliable. Such adjustment is connected with great difficulties in the case of psychotic patients who cannot understand the importance of the given directions; and if the patients take water in excess of the established quantity, the experiments may be entirely misleading. In these studies, moreover, the important point is to see whether the patients under ordinary conditions show abnormalities in the water and salt output. Hence I have employed the same technique as in previous studies on the ammonia metabolism; simultaneously to examine two patients in the same ward under no particular restrictions but under conditions kept as uniform as possible. One of the patients showed an increased output of ammonia, the other a normal output. In the days preceding the experiments, the patients received the ordinary diet of the hospital, and the personnel was instructed not to allow the patients to eat or drink anything beyond this diet. At 7 o'clock the patients were given 1 liter of water, but they received no food before the conclusion of the experiment. The urine was collected every hour till 12 o'clock, and the amount, specific gravity and Na concentrations were determined on each portion of urine.

In addition, determination was made of total N, ammonia N and pH, whereafter the ammonia regulation values were cal-

culated after the formula of Stubbe Teglbjærg and Jørgen Madsen:

$$\alpha = \sqrt{\frac{(\text{pH} - 4.2) \cdot \text{ammonia value} \cdot 10}{4}}$$

TABLE 1.

Excretion of Water and Na in 4 Hours after Intake of 1 Liter of Water in Patients with Hyperammoniuria.

Diagnosis	Specific gravity	Diuresis cc.	Na output mg.
Epilepsy	1032-1004	620	830
"	1023-1004	620	998
"	-1002	975	445
"	1019-1014	321	1066
"	1025-1009	215	416
"	1019-1006	495	823
"	1030-1017	125	548
"	1026-1003	620	501
"	1010-1003	945	956
"	1017-1004	234	439
"	1015-1002	828	476
"	1025-1006	1470	2143
"	1024-1006	1100	1725
"	1013-1003	740	552
"	1017-1004	530	634
"	1022-1002	1160	1018
"	1016-1003	715	
"	1010-1001	1265	
"	1012-	48	
"	-1003	439	
"		45	
"		220	576
"	1018-1001	920	535
"	1027-1005	375	593
Dem. paralytica	-1002	560	619
"	1018-1002	650	528
"	-1002	535	
Dem. præcox	1021-1005	625	1022
"	1014-1002	1275	926
"	1016-1014	160	458
"	1010-1004	350	

(Table 1. Cont.)

Diagnosis	Specific gravity	Diuresis cc.	Na output mg.
Const. psychopathy	1024-1001	1095	
"	1020-1003	960	
Manic depress. psychos.	-1001	955	
" " "	1012-1002	880	
" " "	1021-1001	1620	
Dem. præcox		550	
Neurasthenia	1012-1001	1250	
Dem. præcox	1020-1007	325	
Const. psychopathy	1022-1002	975	
	Average	699	766

TABLE 2.

*Excretion of Water and Na in 4 Hours after Intake of 1 Liter of Water
in Patients with Normoammoniuria.*

Diagnosis	Specific gravity	Diuresis cc.	Na output mg.
Dem. paralytica	1010-1005	1030	1676
"	1016-1003	1470	2767
"	1010-1002	880	559
"	1023-1005	690	884
"	1020-1002	860	1022
"	1013-1003	1030	961
"	1024-1016	630	1737
"	-1023	296	1332
"	1020-1015	470	1042
"	1016-1000	640	1132
"	1022-1001	819	672
"	1020-1005	900	687
"	-1010	230	329
"	1016-1005	810	1397
"	-1001	1655	945
"	1014-1004	1095	2139
"	1021-1006	340	
"	1013-1006	1510	2555
Mental depression	1028-1003	717	727
Const. psychopathy	1014-1011	325	1018

(Table 2. Cont.)

Diagnosis	Specific gravity	Diuresis cc.	Na output mg.
Alcoholic dementia	1020-1002	985	542
Mental depression	1018-1005	635	1005
Const. psychopathy	1021-1004	415	
Dem. præcox	1014-1004	980	1117
Const. psychopathy	1014-1011	325	1018
" "	1018-1005	635	1005
Dem. præcox	1028-1003	950	1937
"	1032-1002	635	590
"	1013-1003	915	852
"	-1004	605	715
"	1016-1007	890	1246
"	-1001	1165	
"	1014-1001	880	
"	-1003	980	
"	1028-1007	705	
"	1014-1012	185	
"	1027-1002	890	
Manic depress. psychos.	1030-1003	635	
" " "	-1002	970	
" " "	1012-1002	940	
" " "	-1002	725	
Const. psychopathy	1029-1002	790	
" "	1028-1003	605	
" "	1012-1007	685	
" "	1015-1004	1115	
" "	1010-1005	440	
" "	1018-1002	815	
" "	1025-1004	710	
" "	1028-1002	1100	
" "	1020-1002	1020	
Epidemic encephalitis	1009-1001	855	
" "	1017-1001	1160	
" "	1020-1005	435	
" "	1024-1002	1310	
" "	1017-1003	820	
Imbecility	1020-1001	1290	
"	1028-1002	595	
Chronic alcoholism	1022-1002	1020	
Average for 58 patients		810	1160

From Tables 1 and 2 it will be noticed that the diuresis on an average is smaller in patients with hyperammoniuria than in those with normoammoniuria, and this difference is even more pronounced with regard to the Na output. Both groups include some patients with high values, however, and some with low values. The difference results from the fact that a low excretion of water and Na is more frequent in patients with hyperammoniuria. According to previous studies, indeed, it was to be expected that a possible retention occurs only periodically, but this circumstance naturally makes it difficult to arrive at any statistically reliable decision on the question. Indeed, the present studies are not to be taken as a positive proof that retention takes place in these patients; yet, to me, they appear in some degree to lend support to this view. For we find:

In 40 patients with hyperammoniuria an average diuresis of 699 cc. and an average Na output of 766 mg.;

in 58 patients with normoammoniuria an average diuresis of 810 cc. and an average Na output of 1160 mg.

It will further be noticed that of the 40 patients with hyperammoniuria the diuresis is less than 600 cc. in 17 patients, *i.e.*, in 42 %, whereas of the 58 patients with normoammoniuria it is less than 600 cc. only in 11 patients, *i.e.*, in 18 % ($d = 0.24 \pm 0.09$).

Of 23 patients with hyperammoniuria the Na output is less than 700 mg. in 14 patients, *i.e.*, in 61 %; and of 29 patients with normoammoniuria the Na output is less than 700 mg. in 6 patients, *i.e.*, in 29 % ($d = 0.40 \pm 0.13$). As far as the Na output is concerned, thus, the difference is greater than 3 times the mean error; so it can hardly be due to accidental circumstances.

As already mentioned, several patients with normoammoniuria show only a small excretion of water. It will be noticed, however, that most of them nevertheless show a considerable Na output; and further, in most of these patients the specific gravity of the urine is seen to fall but slightly during the experiment. Corresponding conditions are seen only to a slight extent or not at all in patients with hyperammoniuria and low diuresis.

Tables 1 and 2 give merely the total output of water and Na in the 4-hour period. But, as mentioned before, the analyses were carried out on portions of urine for a period of 1 hour. For want of space, it is not feasible here to give all these protocols in extenso, but it will be appropriate to cite a few typical examples.

TABLE 3.
Urinary Excretion in a Patient with Normoammoniuria.

Hour	Urine cc.	Sp. gr.	Na mg. %	Na mg.	mg.N in 2 cc.	mg.NH ₃ N in 5 cc.	pH	α
7	590	1013	240		14.0	5.45	5.85	4.2
8	95	1010	180	171	11.6	3.9	5.95	4.0
9	450	1003	36	162	2.0	0.9	6.30	5.2
10	330	1004	116	383	3.4	1.1	6.55	4.7
11	105	1011	233	245	7.7	2.4	6.05	4.0
12	50	—	—	—	12.8	4.0	5.85	3.8
1030				961 +				4.3

TABLE 4.
Urinary Excretion in a Patient with Normoammoniuria and Low Diuresis.

Hour	Urine cc.	Sp. gr.	Na mg. %	Na mg.	mg.N in 2 cc.	mg.NH ₃ N in 5 cc.	pH	α
7	15	—	384		21.7	8.8	5.50	3.8
8	35	—	439	154	21.5	8.4	5.45	3.7
9	6	—	438	26	—	—	5.50	—
10	50	—	436	218	19.0	7.2	5.55	3.8
11	55	—	456	250	18.0	6.7	5.55	3.8
12	150	1023	456	684	17.9	6.7	5.60	3.8
296				1332				3.8

Table 3 illustrates the normal conditions. With the water excretion in the forenoon there is a distinct fall in the Na concentration, and the same applies to the N and NH₃ concentrations. In the two other patients, both with a very low diuresis, a distinct difference is noticed. In the patient with normoammoniuria (Table 4) the Na and N concentrations remain high, so that, for instance, the Na output in mg. in 4 hours is above

TABLE 5.

Urinary Excretion in a Patient with Hyperammoniuria and Low Diuresis.

Hour	Urine cc.	Sp. gr.	Na mg. %	Na mg.	mg. N in 2 cc.	mg. NH ₃ N in 5 cc.	pH	α
7	475	1025	240		27.6	16.0	6.05	5.5
8	20	—	348	69	30.9	10.9	6.75	5.0
9	35	—	298	104	21.4	7.0	7.45	5.4
10	65		153	99	11.1	6.4	7.10	6.9
11	70	1009	120	84	11.4	6.2	6.95	6.4
12	25		240	60	23.0	10.2	6.80	5.7
215				416				5.8

the average, notwithstanding the very low diuresis. In the patient with hyperammoniuria (Table 5) the matter stands quite differently: in spite of the small diuresis we see a fall both in the Na and in the N concentration. So we find that in those patients who have a low diuresis it is only the water that is retained, whereas in patients with hyperammoniuria Na is retained, besides water, and possibly N too. In the control material I found only one patient in whom a low diuresis was associated with a low Na output.

The examination of the urines in one-hour portions was carried out with the additional aim of investigating whether there might be any difference between the two groups as to the points of time for the excretion. This proved not be the case. In these experiments the regulation values showed somewhat greater variations than normally, but no tendency to fall or rise after intake of 1 litre of water.

The present analyses thus indicate that patients with hyperammoniuria periodically have a tendency to retention of Na and, presumably, of N too.

b. *Excretion of Water and Salts after Administration of Diuretics in Patients with Normo- and Hyperammoniuria.*

In continuation of the studies on the water and salt metabolism I have investigated the excretion of water, Na and Cl after administration of salyrgan and theophyllin.

The salyrgan experiments were carried out as follows: Two patients from the same ward—one with hyperammoniuria, the other with normoammoniuria—were examined at the same time. They were not kept on any special diet beforehand. At 9 o'clock 2 cc. of salyrgan was given. At 11 o'clock the patients were given a little water and an apple; otherwise they received no food before 15 o'clock. From 9 to 15 o'clock the urine was collected every hour, and on each portion the amount, Na and Cl output were determined. Besides, the pH was measured; and on the portions from 9, 11, 13 and 15 o'clock the total N and $\text{NH}_3\text{-N}$ were determined for calculation of the ammonia regulation values.

TABLE 6.
Urinary Excretion after Salyrgan Inj. in a Patient with Normoammoniuria.

Hour	Urine cc.	Na mg. %	Na mg.	Cl mg. %	Cl. mg.	pH	mg. N in 2 cc.	mg. NH_3N in 5 cc.	α
8-9	65	412		850		6.20	13.0	3.7	4.0
10	125	399	499	736	920	6.25	8.9	3.2	4.5
11	650	317	2061	531	3452	6.55	1.7	0.5	4.4
12	300	351	1053	545	1635	6.65			
13	290	405	1175	619	1795	6.70	2.7	0.9	4.8
14	90	419	377	835	752	6.65			
15	70	412	288	914	640	6.65	7.4	1.9	4.2
1525			5453		9194				

TABLE 7.
Urinary Excretion after Salyrgan in a Patient with Hyperammoniuria.

Hour	Urine cc.	Na mg. %	Na mg.	Cl mg. %	Cl. mg.	pH	mg. N in 2 cc.	mg. NH_3N in 5 cc.	α
9	45	443		779		7.60	7.3	3.2	6.5
10	150	430	645	1047	1571	5.85			
11	200	424	848	1055	2110	6.65	2.4	1.9	7.4
12	90	435	392	1055	950	6.60			
13	95	444	422	1050	998	7.40	5.5	2.2	6.0
14	40	442	170			8.70			
15	40	450	180	1047	419	8.60	11.8	2.5	5.1
660 cc.			2657 mg. Na		6048 mg. Cl				

For illustration, the experimental protocols will be given in detail for one patient with normoammoniuria and for one patient with hyperammoniuria. (Tables 6 and 7.)

These two examples differ distinctly, the excretion of water, Na and Cl being considerably smaller in the patient with hyperammoniuria than in the other. The total 6-hour excretion for all the patients examined was as follows (Tables 8 and 9):

TABLE 8.
Excretion of Water, Na and Cl in the First 6 Hours after Injection of Salyrgan in Patients with Normoammoniuria.

Pt. No.	Diuresis cc.	Na mg.	Cl mg.
1.	1645	4217	8294
2.	950	3455	5637
3.	1370	3949	7131
4.	1765	5383	21652
5.	1525	5463	9194
6.	940	3584	6499
7.	1315	4002	7813
8.	1510	5861	10125
9.	850	3073	5823
10.	715	2778	3938
11.	1350	4815	7937
Average:	1267	4234	8540

Thus the average excretion is practically the same in the two groups. But among the patients with hyperammoniuria there is a distinct difference between the first 7 patients and the last 7, the former showing a greater excretion of water, Na and Cl than found in the patients with normoammoniuria, while the latter 7 have a much lower excretion. This is presented graphically in Fig. 3.

Furthermore, the last-mentioned 7 patients with hyperammoniuria showed some particular features as to the hydrogen ion concentration of the urine after injection of salyrgan.

In the patients with normoammoniuria (Table 10), pH is found in the first part of the experiments to vary a little within

TABLE 9.

Excretion of Water, Na and Cl in the first 6 Hours after Injection of Salyrgan in Patients with Hyperammoniuria.

Pt. No.	Diuresis cc.	Na mg.	Cl mg.
1	1375	5313	9087
2	1710	5427	9770
3	1524	4549	15742
4	1885	5638	9633
5	1120	4454	7770
6	1630	6209	10332
7	1740	6385	10267
8	1070	2967	
9	660	2657	6048
10	725	2301	3805
11	1050	3869	6042
12	860	3735	5832
13	925	3149	4711
14	465	1586	
Average :	1196	4017	8253

the normal limits, but in the last hours it falls so that in the last analyses it usually is about 5.0. The highest pH in the 15-o'clock portions is 6.6. This is quite in keeping with the clinical

TABLE 10.

Hydrogen Ion Concentration of the Urine after Salyrgan in Patients with Normoammoniuria.

Pt.	At 9	10	11	12	13	14	15 o'clock
1	5.3	5.5	6.3	5.8	5.0	5.0	5.0
2	6.6	5.4	6.6	5.5	5.0	5.0	5.2
3	6.9	6.0	6.3	5.9	5.7	5.9	5.7
4	5.5	5.7	5.7	5.1	5.0	5.1	5.2
5	6.2	6.2	6.5	6.6	6.7	6.6	6.6
6	6.6	5.6	6.5	6.5	5.5	5.4	5.4
7	5.5	5.5	5.6	5.6	5.2	5.0	5.1
8	7.6	6.7	6.5	6.5	4.8	4.8	5.4
9	7.6	7.1	5.5	5.5	5.0	5.0	5.2
10	5.8	5.6	5.8	5.7	5.6	5.9	5.6
11	7.5	6.3	6.0	5.9	5.9	5.9	6.4

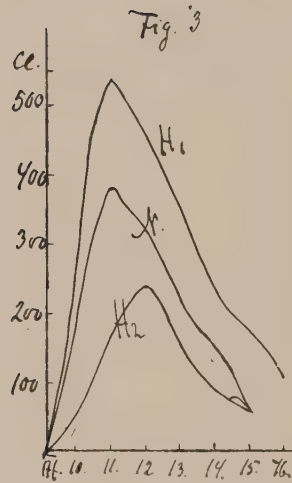


Fig. 3.

Urinary excretion after injection of salyrgan in patients with normo- and hyperammoniuria. In one group of hyperammoniurics (H1) the excretion is greater than in the normoammoniurics; in the other group (H2) it is smaller and delayed.

TABLE 11.
Hydrogen Ion Concentration of the Urine after Salyrgan in Patients with Hyperammoniuria.

Pt.	At 9	10	11	12	13	14	15 o'clock
1	5.7	6.5	5.7	5.7	5.1	5.0	5.0
2	6.8	6.5	6.2	5.4	5.2	5.4	5.5
3	5.7	5.7	6.5	6.4	5.7	5.2	5.4
4	8.3	7.0	6.6	6.5	6.1	5.8	5.6
5	6.0	7.3	6.3	6.1	4.8	4.7	4.8
6	7.3	5.4	6.8	6.7	5.5	5.2	5.6
7	6.6	6.5	6.4	6.3	5.9	5.6	5.6
8	6.5	6.6	6.5	6.8	6.9	7.0	8.3
9	7.6	5.8	6.6	6.6	7.4	8.7	8.6
10	8.6	7.4	6.6	7.2	7.1	7.4	7.3
11	7.3	7.2	6.6	6.7	6.0	6.7	7.5
12	7.2	7.2	6.6	6.9	7.5	7.7	8.6
13	7.1	7.1	6.5	6.8	7.2	7.3	7.4
14	6.5	6.5	6.4	6.2	6.3	6.6	7.3

experience that the urine as a rule is acid under the action of diuretics.

The same findings are seen in the cases of the first 7 hyperammoniurics (Table 11), whereas the last 7 patients show a marked rise in pH instead of a fall, so that pH in all the 15-o'clock portions has reached alkaline values which in some of the patients indicate a degree of alkalinity that is never encountered otherwise except after intake of alkali.

These abnormalities in the hydrogen ion concentration of the urine after administration of salyrgan reminds us of the

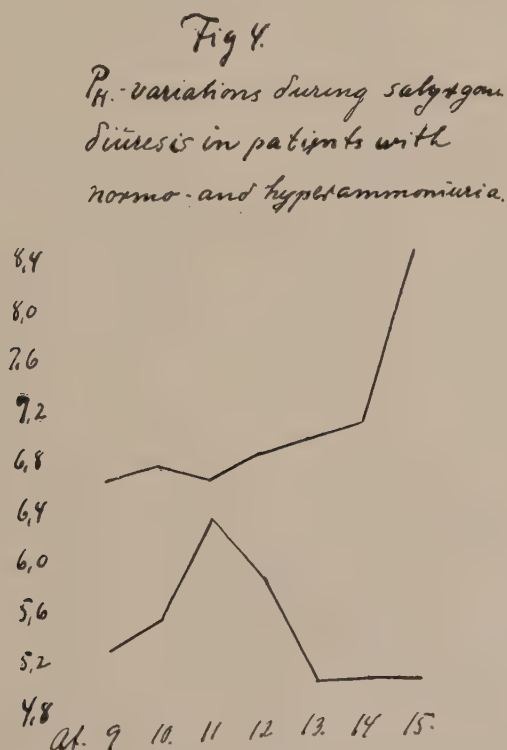


Fig. 4.

Variations of the urinary pH after injection of salyrgan in a patient with normoammoniuria (N) and in a patient with hyperammoniuria. The normoammoniuric shows a rise in pH in the first hours after the injection and then a fall to below 5.0. The hyperammoniuric shows a rise in pH throughout the experimental period, so that the urine after 6-7 hours is strongly alkaline.

"paradoxical acid reaction" in epileptics mentioned by Nørvig & Larsen who have demonstrated that epileptics sometimes react abnormally on acid medicamentation, preserving a high pH in the urine together with an increased excretion of ammonia, sometimes even a rise in pH. There can be no doubt then that epileptics in certain phases of their illness react paradoxically to agencies which in normal subjects give an acid urine. Presumably this is to be interpreted as disturbances in their acid-base equilibrium in alkaline direction.

On calculation of the average urinary excretion for each of the two groups of hyperammoniuric patients, we find:

Pts. Nos. 1-7	1570 cc. urine	5140 mg.Na	10370 mg.Cl.
" " 8-14	822 " "	2894 " "	5288 " "

On comparison of these values with the corresponding values for the patients with normoammoniuria, we find that the hyperammoniurics after the hydrogen ion concentration of the urine can be divided into two groups. In one group, in which the hydrogen ion concentration behaves as in patients with normoammoniuria, the average excretion is greater than in patients with normoammoniuria; in the other group of hyperammoniurics, presenting a divergent behavior of pH, there is a considerably smaller excretion of water, Na and Cl. Thus these experiments show that hyperammoniurics are unstable as to their urinary excretion on administration of salyrgan. In certain periods they excrete abnormally large amounts of water and salts; in other periods they excrete abnormally small amounts. In addition, cases with a tendency to retention also show an abnormal behavior of pH: a marked rise in pH instead of a fall as is seen normally in the course of the diuresis.

On going through the individual experimental protocols, the Na and Cl concentrations of the urine after administration of salyrgan keep practically constant, so that the increase in salt excretion is proportional to the increase in the diuresis.

It will also be appropriate here to enquire whether the various groups show any difference in the rapidity with which the output of urine increases after administration of salyrgan (Tables 12 and 13).

TABLE 12.
Diuresis after Salyrgan in Patients with Normoammoniuria.

Pt. No.	Hours						Total
	9-10	10-11	11-12	12-13	13-14	14-15	
1	215	565	395	240	185	20	1645
2	130	465	185	70	45	25	950
3	110	460	185	360	200	70	1370
4	325	650	420	210	160	—	1765
5	125	650	300	290	90	70	1525
6	50	350	300	100	85	55	940
7	50	370	350	300	170	75	1315
8	200	675	470	180	100	55	1510
9	15	190	325	85	60	40	715
10	60	110	345	180	100	55	850
11	90	125	180	310	520	125	1350
Average	124	387	312	211	156	56	

TABLE 13.
Diuresis after Salyrgan in Patients with Hyperammoniuria.

Pt. No.	Hours						Total
	9-10	10-11	11-12	12-13	13-14	14-15	
1	65	420	490	200	150	35	1375
2	240	725	310	110	160	100	1710
3	25	360	490	280	170	175	1525
4	40	540	625	320	240	140	1885
5	20	450	375	80	100	95	1120
6	50	810	350	165	150	105	1630
7	40	525	600	310	235	70	1740
Average	68	547	463	209	172	103	
8	60	145	490	185	105	35	1070
9	150	200	90	95	40	40	660
10	80	70	155	225	120	75	725
11	85	220	300	340	75	30	1050
12	55	375	210	75	70	75	860
13	85	180	240	120	140	160	925
14	40	60	240	20	90	15	465
Average	79	179	247	151	91	61	

It will be noticed that the normoammoniurics in 8 of 11 experiments showed the greatest output of urine in the second

hour after the injection of salyrgan, whereas 9 out of 14 hyperammoniurics had the greatest output of urine at a later point of time. This phenomenon is most pronounced in the latter group of hyperammoniurics, in whom the total excretion is low. But also the first group of hyperammoniurics shows a tendency to delayed excretion in comparison to the normoammoniurics, notwithstanding the very large total output (Table 13).

In the experiments reported so far, Na has been the only cation mentioned. Indeed, Na makes up by far the greater part of the total cation output. In several of the experiments, however, the potassium excretion was determined at the same time. K was determined after Kramer-Tisdall's method without any preliminary treatment of the urine, which for our purpose is taken to give sufficient accuracy. K was determined on the portion from 8 to 9 o'clock (before injection of salyrgan) and on

TABLE 14.
Urinary Na and K Output after Salyrgan in Patients with Normoammoniuria.

Portion from	Amount cc.	Na mg. %	Na mg.	K mg. %	K mg.
8-9	65	412	268	99	65
10-11	650	317	2061	14	92
8-9	60	346	208	369	222
10-11	350	352	1232	27	94
8-9	40	244	98	162	65
10-11	240	347	833	39	120
8-9	50	354	177	326	163
10-11	675	328	2214	24	162
8-9	20	362	72	304	61
10-11	325	374	1216	40	130
8-9	50	368	184	359	179
10-11	345	330	1139	32	110
8-9	140	361	575	70	98
10-11	440	322	1417	16	70
8-9	70	477	334	226	158
10-11	520	343	1784	58	302

the portion from 10 to 11 o'clock, when the urinary output usually reached its maximum (Tables 14 and 15).

TABLE 15.
Urinary Na and K Output after Salyrgan in Patients with Hyperammoniuria.

Portion from	Amount cc.	Na mg. %	Na mg.	K mg. %	K mg.
8-9	20	340	68	462	92
10-11	450	357	1607	19	86
8-9	60	472	283	133	80
10-11	820	339	2745	4	32
8-9	100	267	267	36	36
10-11	300	357	1062	1	13
8-9	35	406	142	199	70
10-11	375	406	1523	31	116
8-9	40	459	183	64	26
10-11	600	358	2188	13	78
8-9	30	314	94	143	43
10-11	240	339	814	17	41

From Tables 14 and 15 it will be noticed that the effect of salyrgan on the Na excretion differs from that on the K output. The Na concentration of the urine keeps practically constant, so that the increased diuresis gives a corresponding increase in the Na output. On the other hand, there is a marked fall in the K concentration, so that the K output in the hour before the injection of salyrgan is of about the same magnitude as in the period of 10-11 o'clock. This is in keeping with the findings in previous investigations, according to which the intracellularly deposited K is susceptible to the influence of diuretics only in a slight degree as compared to Na, which is chiefly deposited extracellularly. In this respect the findings in the two groups were fairly alike, although the tendency to a fall in the K concentration is greater in hyperammoniurics. In two of the experiments the urine thus became almost free from potassium during the experimental diuresis. It is to be

mentioned that the patient with a K output of only 3 mg. in the urine portion from 10-11 shortly after had an epileptic seizure. So there seems perhaps to be some reason to investigate the K excretion in epileptics more closely, but this would fall outside the scope of the present work. These studies show, however, that in comparison to the Na output the excretion of potassium under increased diuresis is quantitatively insignificant.

*On the Excretion of Water and Salts after Intake
of Theophyllin.*

The studies here presented on the urinary excretion after intake of water and after injection of salyrgan show then that the output of water as well as salts is temporarily diminished in patients with hyperammoniuria—chiefly epileptics. This confirms the findings in several previous investigations on the water and salt metabolism in epilepsy. Thus, Yde found that epileptics respond to theophyllin in a lesser degree than do non-epileptics. He examined 78 epileptics and found the effect of theophyllin to be absent in 16, *i.e.*, in about 25 %. In 93 non-epileptics he found the theophyllin effect to be absent in 10. Considering the size of his material, this difference is of real significance, and Yde further emphasizes that his control material was not as good as might be desirable as several of his control patients were suffering from various mental affections, so that some of them possibly may have had cerebral lesions giving rise to similar disturbances as encountered in epileptics—inasmuch as Yde thinks the abnormality is due to an affection of the hypothalamus.

In connection with the salyrgan experiments I also examined some epileptics with hyperammoniuria to whom I gave theophyllin employing essentially the experimental technique adopted by Yde. For two days prior to the experiment, the patients were kept on a standard diet described on p. 269. On the days of the experiment they were confined to bed. At 8 o'clock they received 200 cc. of water, and in the following 4 hours the urinary excretion was examined. Yde pooled the

total output of urine for this period, measured the amount and determined the Cl content. In some of the experiments I have collected the urine in portions for every hour so as to be able further to analyze the excretion in the course of the experiment. Besides the Cl output, I also determined the Na excretion.

After 12 o'clock on the first experimental day, the patients were given the ordinary standard diet. The next day the experiment was continued with this difference, that, besides 200 cc. of water, the patient was also given 8 mg. of theophyllin per kg. of body weight at 8 o'clock. The following day, in some of the experiments I have repeated the test by giving 200 cc. of water + 1 cc. pitressin subcutaneously.

The examination of 12 epileptics with hyperammoniuria gave the following results for the total 4-hour excretion (Table 16):

TABLE 16.
*Urinary Excretion after Intake of Water and Theophyllin
in 12 Epileptics with Hyperammoniuria.*

After 200 cc. water			After theophyllin			Difference		
Diuresis cc./kg.	Na cg./kg.	Cl cg./kg.	Diuresis cc./kg.	Na cg./kg.	Cl cg./kg.	Diuresis cc./kg.	Na cg./kg.	Cl cg./kg.
3.7	1.16	2.33	11.3	4.28	6.91	7.6	3.21	4.58
2.2	0.89	1.60	8.3	3.83	6.43	6.1	2.94	4.83
2.6	0.92	1.96	4.4	2.01	3.44	1.8	1.09	1.48
2.7	1.25	2.98	10.4	3.22	7.37	7.7	1.97	4.45
1.8	0.57	0.90	4.3	1.79	2.78	2.5	1.22	1.88
2.0	1.00	2.11	5.0	2.59	5.16	3.0	1.59	3.05
0.9	0.14	0.43	7.2	3.30	5.87	6.3	3.16	5.44
2.9	0.87	2.02	8.0	3.39	5.59	5.1	2.52	3.57
3.6	1.70	3.46	9.2	4.51	7.83	5.6	2.81	4.37
3.9	1.12	1.68	12.2	4.93	7.14	8.3	3.81	5.46
1.7	0.68	1.15	8.2	3.62	5.68	6.5	2.94	4.53
7.6	2.21	4.43	11.8	4.43	6.67	4.2	2.22	2.24

Yde reckons that a difference in the diuresis of less than 2 cc./kg. and a difference in Cl of less than 2 cg./kg. can be regarded as lacking theophyllin effect. Accordingly, among my 12 examined patients two were lacking this effect and one was

on the border-line, which corresponds fairly well to the findings of Yde. Numerically no particular significance is to be attached to my material, but in my examinations one fact was found to suggest that the outcome was not due to accidental circumstances. Chance would that one of the patients had an epileptic seizure during the theophyllin experiment, namely at 9.55 o'clock. This was the patient recorded as No. 3, that is, the very patient who showed the slightest theophyllin effect. In this patient I had also determined the Na and Cl concentration of the serum during the experiment and found the following values:

At 8,30	272 mg.% Na and 426 mg.% Cl
" 9,15	240 " " " 342 " "
" 11,00	345 " " " 376 " "

This patient thus showed a marked fall in the Na and Cl concentrations in the serum after the intake of theophyllin. So, in the preparoxysmal period we find an absence of the usual theophyllin effect on the excretion of water, Na and Cl and, at the same time, a marked decrease in the Na and Cl concentrations in the blood.

The Na and Cl contents of the serum were determined also in some of the other experiments. In some of them, unfortunately, I was unable to examine more than a couple of blood samples in the 4-hour experimental period, so that the recovered minimum values possibly do not represent the absolute minimum in the given cases. As mentioned already, the Na and Cl concentrations in the serum vary rather irregularly during the theophyllin test, and to find the absolute minimum value, therefore, it is necessary to take samples of the blood at short intervals—every half-hour or even more frequently—throughout the experiment. For me this was impracticable with the assistance I had at my disposal.

c. Relation between the Theophyllin Effect and the Na and Cl Contents of the Serum.

Table 17 shows that there is no absolute proportionality between the theophyllin effect and the Na and Cl concentrations

in the serum. Yet the three patients with a theophyllin effect on the urinary Na output of less than 2.0 cg. per kg. of body weight show a great decrease in serum Na; and the patient with a theophyllin effect on the urinary Cl output of less than 2 cg. per kg. of body weight shows a low value for serum Cl. These 3 patients had epileptic seizures in immediate connection with the experiments. In patient No. 4, who likewise had a seizure but not till 14 o'clock, the serum Na is decreased and the serum Cl a little low, but the theophyllin effect is good. In the three patients who had no seizure in connection with the experiments, the theophyllin effect is good, and the values for serum Na and Cl are normal.

TABLE 17.

Relation between the Theophyllin Effect and the Na and Cl Contents of the Serum.

(Theophyllin is given at 8 a. m.).

Pt. No.	Theophyllin effect			Minimum serum values under theophyllin		Remarks
	Urine cc./kg.	Na cg./kg.	Cl cg./kg.	Na cg./kg.	Cl cg./kg.	
1	1.8	1.09	1.48	240	342	Epileptic seizure at 9.55.
2	7.7	1.97	4.45	279	365	Epileptic seizure at 13 o'clock.
3	2.4	1.54	2.32	297	357	Several convulsive attacks at noon.
4	8.3	3.81	5.46	276	361	Epileptic seizures at 14 o'clock.
5	6.1	3.16	5.44	328	391	No attack on day of experiment.
6	5.6	2.81	4.37	315	381	" " " " " "
7	4.2	2.22	2.24	327	379	" " " " " "

These findings are thus in keeping with the modern theories about the kidney function, according to which the chlorine excretion as well as the sodium excretion are dependent on the function of the tubuli. If the serum Na or Cl concentration falls below a certain limit, the tubuli will reabsorb the greater part of the amounts of Na and Cl filtered out in the glomeruli. Thus, Rehberg thinks that if plasma Cl falls to 370 mg.%, reabsorption of the chlorine will take place. Van Slyke gives a

somewhat lower limit: 350 mg.%. The above experiments are rather in keeping with the latter value.

As mentioned already, some of the experiments were concluded with a subcutaneous injection of 1 cc. of pitressin at 8 o'clock on the day after the theophyllin test. Otherwise the experimental technique was the same as for the two preceding days.

d. *Effect of Pitressin in Epileptics with Hyperammoniuria and in non-Epileptics with Normoammoniuria.*

The two groups of patients recorded in Table 18 show that the urinary excretion is inhibited after injection of pitressin. This does not apply to the third control patient whose urinary excretion was the same after pitressin as on the day of the control test.

TABLE 18.
Effect of Pitressin on the Urinary Excretion.

Pt. No.	After 200 cc. of Water			After pitressin			Difference		
	Urine cc /kg.	Na cg./kg.	Cl cg./kg.	Urine cc./kg.	Na cg./kg.	Cl cg./kg.	Urine cc /kg.	Na cg./kg.	Cl cg /kg.
<i>Epileptics with Hyperammoniuria.</i>									
1	3.7	1.16	2.33	0.8	0.07	0.55	-2.9	-1.08	-1.78
2	2.2	0.89	1.60	1.1	0.28	0.42	-1.1	-0.61	-1.18
3	2.6	0.92	1.96	1.7	0.32	1.06	-0.9	-0.60	-0.90
4	2.7	1.25	2.92	1.3	0.21	0.63	-1.4	-1.04	-2.39
Average							-1.6	-0.83	-1.39
<i>Non-epileptics with Normoammoniuria.</i>									
1	11.1	1.10	1.81	2.5	0.95	2.09	-8.6	-0.15	+0.28
2	2.2	0.80	1.96	1.8	0.70	2.03	-0.4	-0.10	+0.09
3	2.4	0.96	1.29	2.4	0.97	1.69	0	+0.01	+0.40
Average							-2.2	-0.06	+0.19

The epileptics further show a decrease in the excretion of Na and Cl—something that is not seen in the control patients.

This difference in the reaction to pitressin becomes even more conspicuous on consideration of the absolute output of urine and the salt concentration (Table 19).

TABLE 19.
*Diuresis and Na and Cl Concentrations of the Urine after
Injection of Pitressin.*

Pt. No.	After 200 cc. of Water			After pitressin		
	Diuresis in 4 hrs.	Na mg. %	Cl mg. %	Diuresis in 4 hrs.	Na mg. %	Cl mg. %
<i>Epileptics.</i>						
1	255	318	633	57	100	680
2	166	404	723	85	248	372
3	175	352	746	115	184	600
4	190	453	1055	90	164	481
<i>Control Patients.</i>						
1	535	99	163	120	391	842
2	180	372	877	145	400	1127
3	205	405	549	205	380	709

In the control patients it will be noticed that the inhibition of the diuresis is accompanied by an increase in the Na and Cl concentrations in the urine, so that the absolute amounts of Na and Cl excreted are unchanged. This phenomenon is well-known from previous investigations, as pitressin does not inhibit the reabsorption of Na and Cl.

Other conditions are found in the epileptics, however. Here the inhibition of the diuresis is accompanied by a decrease in the Na and Cl concentration, more pronounced for Na. The result is therefore a considerable reduction in the excretion of Na and Cl.

So, all the present studies on the urinary excretion after water intake, theophyllin, salyrgan and pitressin indicate that epileptics have periodically a tendency to retention, not only of water but also of Na and Cl, and this is most pronounced for the electrolytes.

e. *Proportion of the Na and Cl Output in the Urine under Various Circumstances.*

In earlier investigations on the salt metabolism it was customary to limit the analysis to the amount of Cl and then from this to calculate the amount of NaCl, as it was taken for granted that these two ions were present in equivalent amounts in the various biological fluids as urine, blood, etc. Subsequent investigations have demonstrated that this is far from being a constant rule. Thus, oedemata, transudates and exudates contain more Cl than Na, so that the formation of these morbid products implies a shift in the Cl/Na quotient in the urine. It has been asserted, too, that various lesions of the liver bring about some shifts in the mutual proportion of these ions. Hence it is essential to investigate both Na and Cl in order to obtain a reliable idea about the excretory conditions.

In the present studies, one of the principal aims has been to investigate whether there be any established relation between the salt metabolism and the ammonia excretion, and here, of course, it has been particularly essential to determine the output of both Na and Cl. If, for instance, a part of the sodium from the NaCl ingested with the food is retained in the organism, an excess of Cl will be excreted, and more ammonia will then be required, as Cl can be excreted only in combination with alkali metals or in the form of ammonium salts.

Through preliminary analyses it was realized that the Cl/Na quotient (calculated in equivalents) under different conditions might undergo not inconsiderable variations; in order to obtain a reliable basis for comparison between various categories of patients it was necessary, therefore, to examine the patients under standard conditions. Prior to the examinations the patients were kept on a standard diet—in particular as to its water and salt contents—for two days before the experiment. On the day of the experiment the patient was told to void at 7 o'clock and at 8, and the latter portion of urine was used for the analytical material. The patient was fasting and had taken no fluid before 8 o'clock.

Under these experimental conditions the findings recorded in Table 20 were obtained in control patients with normal ammonia output.

TABLE 20.

Proportion between the Urinary Output of Na and Cl in Patients with Normoammoniuria under Standard Conditions.

Pt. No.	mg.eq.Na	m ^l g.eq.Cl	Cl/Na	Cl excess	α
1	4.5	5.0	1.1	0.5	5.2
2	8.0	9.0	1.1	1.0	5.5
3	4.8	5.4	1.14	0.6	
4	9.1	9.9	1.01	0.8	
5	3.3	5.4	1.6	1.1	
6	2.2	3.6	1.6	1.4	
7	9.6	11.6	1.2	2.0	
8	2.8	4.5	1.6	1.7	
9	8.0	8.6	1.1	0.6	
10	1.9	2.5	1.3	0.6	4.7
11	50.0	52.3	1.04	2.3	4.6
12	58.5	48.9	0.83	9.6	4.6
13	22.2	47.1	2.12	5.1	4.7
14	24.8	27.8	1.12	3.0	4.8
15	31.5	36.1	1.14	4.6	5.6
16	41.7	52.0	1.24	10.3	5.2
			1.26	2.9 mg.eq.	

Under the same experimental conditions, epileptics with hyperammoniuria gave the findings recorded in Table 21.

As seen from Table 20, the ratio between equivalent amounts of Cl and Na in the control patients varies between 0.83 and 2.12, averaging 1.26. In the epileptics with hyperammoniuria this ratio varies between 0.49 and 3.2, averaging 1.55. In the 16 control patients, Cl/Na is over 1.3 in 4 cases, whereas in 35 epileptics the Cl/Na ratio is over 1.3 in 22 cases. On an average the Cl excess is 2.9 in the controls, 6.3 in the epileptics. Thus there is ascertained an increased Cl excess in the epileptics, which is due to the fact that high values are more frequent here whereas some of the values are just as low as those observed in the controls.

TABLE 21.

Proportion between the Urinary Output of Na and Cl in Epileptics with Hyperammoniuria under Standard Conditions.

Pt. No.	mg.eq.Na	mg.eq.Cl	Cl/Na	Cl excess	α	Remarks
1	6.0	15.7	2.61	9.7	7.2	
2	12.4	12.3	0.9	—0.1	7.0	
3	40.9	52.2	1.28	11.3	5.8	
4	4.3	6.3	1.46	2.0		
5	7.0	9.7	1.40	2.7		
6	11.8	16.1	1.36	4.3		Attack at 9,55
7	7.6	13.2	1.73	5.6		
8	12.5	24.3	2.0	11.8		
9	1.6	3.4	2.1	1.8		
10	54.6	62.8	1.1	8.2		
11	7.2	7.3	1.0	0.1		
12	74.4	94.0	1.3	19.6		
13	0.43	1.4	3.2	1.0		
14	0.73	2.4	3.2	1.7		
15	3.4	5.0	1.4	1.6		
16	4.8	6.6	1.4	1.8		
17	4.2	6.5	1.5	2.3		
18	1.9	4.4	2.3	2.5		
19	30.7	29.9	1.0	— 0.8		Attack at 14,00
21	2.0	4.0	2.0	2.0		
22	1.8	2.9	1.6	1.1		
23	2.3	3.6	1.6	1.3		
24	13.2	15.9	1.1	2.7		
25	33.6	38.6	1.06	5.0	6.4	Attack at 3,00
26	72.5	99.7	1.36	27.2	5.6	
27	5.7	12.1	2.12	6.4	5.4	
28	22.5	28.3	1.25	5.8	6.5	
—	4.9	2.4	0.49	— 2.5	6.0	Attack at 7.15
29	35.4	54.5	1.53	19.1	7.1	
30	59.7	87.1	1.46	26.4	6.8	
31	18.3	23.9	1.30	5.6	6.7	
32	3.5	5.7	1.62	2.2	5.3	
33	6.8	10.0	1.5	3.2		
34	39.5	51.1	1.3	11.6		
35	18.0	41.1	2.3	23.1		
			1.55	6.3 mg.eq.		

In several experiments the regulation value was determined at the same time and it turns out that there is no definite relation between Cl/Na and α . Nor was this to be expected in such experiments, as we know that it takes a certain length of time for the ammonia production to adjust itself after the acid excretion. Still, the temporary Cl excess in relation to Na will probably stimulate the ammonia production so that the increased ammonia output in the epileptics may be attributable to the abrupt changes in the Cl and Na excretion.

TABLE 22.

Cl/Na Ratio in the Urine under Theophyllin.

Patients with Normoammoniuria.

	Before theophyllin	Under theophyllin (8 mg pr. kilo)
No. 1.	1.37	1.1—1.01—0.96—1.06—1.11
„ 2.	1.1	1.1—1.18—1.05—1.03—1.13
„ 3.	1.08	1.09
„ 4.	1.60	1.3
„ 5.	1.60	0.9
„ 6.	1.30	1.0
Average	1.34	1.07

Patients with Hyperammoniuria.

	Before theophyllin	Under theophyllin
No. 1.	0.9	0.98—1.0—1.1—1.17
„ 2.	1.46	1.02—1.0—1.0—1.26—1.31
„ 3.	1.36	1.24—0.98—1.25—1.18
„ 4.	2.0	1.48
„ 5.	1.1	1.0
„ 6.	1.3	1.3
„ 7.	3.2	1.1
„ 8.	1.4	1.1
„ 9.	2.3	1.1
„ 10.	2.0	0.9
„ 11.	1.6	1.0
„ 12.	1.3	0.98
Average	1.66	1.11

In order further to investigate the significance of the ratio Cl/Na, I have investigated its behavior under various conditions as, for instance, administration of theophyllin and pitressin (Tables 22 and 23).

Thus we see a fall in the Cl/Na ratio under the influence of theophyllin both in the controls and in epileptics with hyperammoniuria. In both groups the average value is lowered about 1.1. Owing to the higher initial value in the epileptic group, the fall is greater here.

TABLE 23.
Cl/Na Ratio in the Urine under Pitressin.

	Before pitressin.	Under pitressin. (1 cc.)
<i>Controls.</i>		
No. 1.	1.3	3.3—1.2—1.0—1.04
„ 2.	2.0	3.3—3.1—7.1—6.0
<i>Epileptics.</i>		
No. 1.	5.8	6.5—2.6—5.2—9.0
„ 2.	4.9	2.9—0.8—0.56—0.53
„ 3.	3.0	2.8—1.8
„ 4.	3.6	1.9

The values obtained for Cl/Na are very high, both before and after the injection of pitressin. Some patients show a marked rise in this value after pitressin, others show a fall. Presumably the high initial values are connected with the circumstance that this experiment was performed on the day after the theophyllin test. So it is impossible here to decide what influence pitressin has had on the results. It can merely be established that on the day after the theophyllin diuresis the patients showed an excessively high Cl/Na ration after injection of pitressin, that is, under conditions where the excretion of water, Na and Cl was slight.

From this it is evident that Cl/Na is low when the excretion of water, Na and Cl is high—as, for instance, after intake of

theophyllin—and Cl/Na is high when the excretion of water, Na and Cl is slight—as in the morning after theophyllin diuresis and after injection of pitressin. From these findings it may be assumed that a high Cl/Na ration indicates that the patient is in a retention phase. If this be correct, the more frequent occurrence of a high Cl/Na ratio in epileptics means that they often are in a retention phase.

It is to be mentioned that all these examinations were carried out on patients under standard conditions. Determination of the ratio without preliminary adjustment of the patients shows such wide variations in the controls too as to make it impossible to interpret the results.

Then the behavior of the Cl/Na ratio under hyperventilation was looked into. The findings are recorded in Table 24.

TABLE 24.

Pt. No.	Before Hyperventilation			After Hyperventilation		
	mg.eq.Na	mg.eq.Cl.	Cl/Na	mg.eq.Na	mg.eq.Cl.	Cl/Na
1	5.7	12.1	2.12	3.7	4.3	1.16
2	3.6	4.8	1.3	29.9	22.8	1.1
3	13.8	14.6	1.0	12.5	8.8	0.7
						(absences)

All three cases thus show a fall in Cl/Na under hyperventilation. In Patient No. 3, who had a couple of absences under the hyperventilation, this ratio is particularly low.

Cl/Na Ratio under Convulsive Attacks.

In a few cases, specimens of urine have been obtained shortly before and after epileptic attacks of convulsions. As specimens of urine always, even under the most favorable conditions, represent the production of urine through some length of time, seldom less than half an hour, their examination can never be limited to demonstrate the actual conditions immediately before and after the seizures. But if we have a number of specimens voided before and after the attacks, they may possibly reveal some interesting feature (Table 25).

TABLE 25.
Cl/Na Ratio in the Urine before and after a Seizure.

Urine voided before		Seizure at	Urine voided after		Remarks
Hour	Cl/Na		Hour	Cl/Na	
12,00	1.21	12,15			
9,00	1.24	9,55	10,00	0.98	Under theophyllin
12,00	1.48	13,00			Under theophyllin
		3,00	7,00	1.06	
7,00	1.25	7,15	8,00	0.49	
8,00	1.00	8,07	8,15	0.70	Under hyperventilation
		8,00	9,10	1.13	
10-11	1.7	10,45	11-12	1.6	After salyrgan
11-12	1.0	11,46	12-13	1.0	After salyrgan

Thus the Cl/Na ratio is found to be low round the juncture for the epileptic seizure, particularly after the attack. An exception to this is seen in the last case but one, and it is to be mentioned that this patient was not adjusted to a water and salt equilibrium prior to the experiment. The same applies to the last patient.

III. RELATION OF THE AMMONIA OUTPUT TO THE SALT METABOLISM

The preceding studies have shown the presence of some abnormalities in the water and salt metabolism of hyperammoniurics, especially in epileptics, indicating that the regulation of the electrolytic equilibrium is less precise in these subjects. The demonstrated changes are explained most easily as due to periodical reductions in the amounts of available electrolytes, whether this results from a universal salt deficiency in the organism or a temporary abnormal fixation of salts, especially Na, by the tissues. Further, this abnormality appears not to be connected with a kidney function but with the depot function of the tissues; and it seems reasonable to assume that water, Cl and Na are retained periodically by the tissues, so that,

for instance, the excretion of these substances is smaller than normally on administration of diuretics.

Presumably an increased diuresis is associated with an increased excretion of strong acids—besides Cl, also sulphates and organic acids—it is rather probable that even though the lowered Na output is accompanied by a decreased Cl excretion, it will bring about a shift in the proportion of strong acids and solid alkalies, so that there are not sufficient amounts of solid alkalies at the disposal of the acid excretion, and hence it is necessary for the organism to produce particularly large amounts of ammonia. This might offer the proper explanation of the increased ammonia output in epileptics. It was reasonable, therefore, to investigate whether there be any definite relation between the ammonia output and the excretion of water and salts.

a. *Relation between the Ammonia Regulation Value and Excretion of Water and Salts.*

This question is elucidated by the findings recorded in Table 26. Thus there does not seem to be any constant relation between the water and salt excretion and the ammonia regulation values at the commencement of the experiment, as there are cases with a large output of water and salts and a small regulation value, as well as subjects with a small output of water and salts and a high regulation value. Thus, epileptics with large excretion often show a considerably higher regulation value than is found for normal subjects with a considerably lower excretion. If, on the other hand, we consider all epileptics alone, it will be noticed that epileptics with a low excretion on an average show a considerably higher regulation value than patients with a large excretion. Among the patients with a low excretion, the highest regulation value is found in the patient with the lowest excretion and the lowest regulation value is found in a patient with a high excretion.

On comparison of the findings in the normal controls and in epileptics with a large output, these experiments appear to disprove any causal connection between the magnitude of the

TABLE 26.
*Water, Na and Cl Output in 6 hours after Salyrgan and
 the Initial Regulation Value.*

	Urine cc.	Na. mg.	Cl. mg.	α
<i>1. Controls with Normoammoniuria.</i>				
	1645	4217	8294	4.2
	950	3455	5637	3.6
	1370	3949	7131	4.4
	1765	5383	21652	4.6
	1525	5453	9194	4.0
	940	3584	6499	4.2
	1315	4002	7813	4.0
	1510	5861	10125	3.6
	715	2778	3938	3.8
	850	3073	5823	3.8
	1350	4815	7937	3.6
Average	1267	4234	8540	4.1
<i>2. Epileptics with large excretion.</i>				
	1375	5313	9087	5.6
	1710	5427	9770	5.0
	1525	4549	15742	5.4
	1885	5638	9633	4.3
	1120	4454	7770	5.5
	1630	6209	10332	4.1
	1740	6385	10267	5.4
Average	1570	5140	10370	5.0
<i>3. Epileptics with small excretion.</i>				
	1070	2967		5.5
	660	2657	6048	6.5
	725	2301	3805	5.4
	465	1586	2805	7.8
	1050	3869	6042	4.7
	860	3735	5832	5.6
	925	3149	4711	5.2
Average	822	2894	5288	5.8

output and the ammonia regulation values. It is to be kept in mind, however, that here we are dealing with very complicated

conditions. When some epileptics on the experimental day give relatively low regulation values—3 of them even so low as to fall within the normal limits—it does not mean that they always have regulation values of this magnitude; nor does a large output mean that the patient always excretes corresponding amounts. The values merely represent various phases. We know that the increase in ammonia output after intake of acid makes its appearance only after a certain latent period, depending on the available amount of solid alkalis in the organism. It is not to be expected, therefore, that the initial ammonia regulation value will depend on a possible tendency to retention on the day of the experiment, for here the regulation value is more likely to be an expression for the prevailing conditions on the day before or perhaps even further back.

So the question about a connection of the regulation values and a tendency to retention cannot be solved conclusively in this way. Still the experiments show that the epileptics with their instability of excretion give higher ammonia regulation values than found in normal subjects, and epileptics in the retention phase give higher ammonia regulation values than epileptics in the excretory phase. The actual solution of the question will require systematic determination of all acid and alkaline elements in the urine through a considerable length of time and simultaneous determination of the relative ammonia output.

b. *The Relative Ammonia Output (Regulation Value) under Influence of Salyrgan.*

In normal patients the diurnal variations of the regulation value is very small. It happens but extremely seldom that 10 determinations of a on the same patient on 10 consecutive days show a difference of more than 1.0 between the smallest and highest values. Examination of 49 patients has shown an average amplitude of 0.52 (dissertation). In epileptics the variations are considerably higher, as a rule exceeding 1.0. In 46 epileptics the average amplitude was found to be 1.33. The analyses cited here were carried out on night urines. Urines examined in portions

at intervals of 1 hour in the course of the day show practically the same features, only a slightly larger amplitude. It is essential to be acquainted with these facts when one wishes to investigate whether a ammonia regulation value is subject to abnormal variations under other conditions—for instance, under the influence of diuretics.

TABLE 27.

Variations of the Regulation Value on Intake of 1 Liter of Water at 7 a. m.

Diuresis from 7 a. m. to 12	mg. Na	Regulation value						Amplitude
		at 7	8	9	10	11	12	
880	559	4.5	4.6	4.3	3.8	4.1	3.8	0.8
690	884	4.3	4.6	4.1	4.5	4.8	4.9	0.8
860	1022	4.0	4.3	5.1	5.2	—	5.0	1.2
560	619	5.3	5.0	5.2	4.1	4.1	4.0	1.2
1030	960	4.2	4.0	5.2	4.7	4.0	3.8	1.4
1510	2555	4.8	5.1	4.7	5.3	5.0	5.2	0.6
630	1737	4.0	4.0	4.1	4.2	4.2	4.4	0.4
296	1332	3.8	3.7	—	3.8	3.8	3.8	0.1
470	1042	3.7	3.9	4.8	4.5	4.6	4.5	0.8
640	1132	3.4	3.5	3.5	3.5	3.6	3.5	0.2
Average		4.2	4.3	4.5	4.5	4.2	4.3	0.7

As will be noticed, in normal persons no abnormal variations of the regulation value is produced by the intake of 1 liter of water. The variations have a tendency to be smaller in persons with a relatively large Na output.

Similar studies on epileptics gave the results reported in Table 28.

In the epileptics, it will be noticed, the variations of the regulation values after intake of water are somewhat greater than those encountered in the controls, it is true, but not greater than seen in epileptics without intake of water. So, the intake of 1 liter of water is not able in these patients to produce an abnormal shift in the relative ammonia output.

For comparison with the results obtained with intake of water in the control patients, it will be noticed that the varia-

TABLE 28.

Variations of the Regulation Value in Epileptics on Intake of water.

Diuresis from 7 a. m. to 15	mg. Na	Regulation value						Amplitude
		at 7	8	9	10	11	12	
220	578	5.2	5.0	—	5.4	3.7	4.2	1.7
590	884	6.6	5.1	6.2	6.9	6.4	6.0	1.8
720	830	6.5	6.4	5.7	4.9	4.2	4.5	2.3
320	1066	4.1	3.4	4.7	4.8	4.2	5.2	1.8
975	445	5.1	—	3.9	3.9	3.9	3.5	1.6
215	416	5.5	5.0	5.4	6.9	6.4	5.7	1.9
495	823	5.0	4.9	5.3	5.5	5.2	5.0	0.6
125	548	4.7	4.5	5.0	4.9	5.0	4.9	0.5
620	501	4.7	5.7	6.1	6.0	5.3	5.5	1.3
945	956	5.6	5.2	6.1	6.0	5.6	5.6	0.9
235	439	5.2	4.9	4.9	4.9	4.9	5.2	0.3
1470	2143	5.3	5.1	5.3	4.7	5.1	5.0	0.6
1100	1725	5.0	5.4	5.9	6.3	5.3	5.7	1.3
Average		5.3	5.0	5.4	5.5	5.0	4.8	1.3

TABLE 29.

Variations of the Regulation Value after Injection of Salyrgan in Control Patients.

Diuresis from 9 to 15	mg. Na	mg' Cl	Regulation value					Amplitude
			At 9	10	11	12	13	
1645	4217	8294	4.2	—	5.2	4.2	4.5	1.0
950	3455	5637	3.6		5.0	3.5	3.5	1.5
1370	3949	7131	4.4		5.5	6.0	4.4	1.6
1765	5383	21652	4.6		2.5	2.8	1.7	2.9
1525	5453	9194	4.0	4.5	4.4	4.8	4.2	0.8
940	3584	6499	4.2	3.2	4.6	4.5	3.7	1.4
1315	4002	7813	4.0	3.7	4.2	4.2	3.7	0.5
1510	5861	10125	3.6	5.2	7.2	3.0	2.7	4.5
715	2778	3938	4.8	4.5	4.8	4.7	5.0	0.5
850	3073	5823	3.8	4.8	4.6	4.2	4.4	1.0
1350	4815	7937	3.6	4.3	4.0	4.4	4.0	0.8
Average			4.1	4.3	4.7	4.2	3.7	1.5

tions of the regulation values are decidedly greater after injection of salyrgan, the average amplitude being twice as great in the latter experiments. Apart from one exception, we find

a low initial regulation value, at 9 a. m., rising in the first 2-3 hours of the experimental period and then falling off, so that at 15 o'clock the value is below the initial level. Considering the average values, we find the maximum at 11 o'clock, with an increase of 0.6, and then a fall till 13 o'clock, amounting to 1.0.

TABLE 30.
*Variations of the Regulation Value after Injection of Salyrgan
in Epileptics.*

Diuresis from 9 to 15	mg.Na	mg.Cl	Regulation value					Amplitude
			At 9	10	11	13	15	
1375	5313	9087	5.6	—	6.1	5.2	4.9	1.2
1710	5427	9770	5.0	—	6.5	5.2	5.0	1.5
1525	4549	15742	5.4	—	6.1	3.5	4.3	2.6
1885	5638	9633	4.3	4.8	6.0	6.4	4.6	2.1
1120	4454	7770	5.5	5.0	6.5	4.0	3.9	2.5
1630	6207	10332	4.1	4.7	5.9	4.3	3.7	2.2
1740	6385	10267	5.4	—	6.3	6.7	4.5	2.2
Average			5.0	4.8	6.2	5.0	4.4	2.0
1070	2967		5.5	—	5.7	5.8	4.6	1.2
660	2657	6048	6.5	—	7.4	6.0	5.1	2.3
725	2301	3805	5.4	6.4	6.9	6.0	6.2	1.5
465	1568	2805	7.8	7.1	7.0	8.2	6.7	1.5
1050	3869	6042	4.7	4.8	5.9	5.4	3.6	2.3
860	3735	5832	5.6	5.7	6.3	6.3	5.1	1.2
925	3149	4711	5.2	5.0	6.2	5.6	4.1	2.1
Average			5.8	5.8	6.5	6.2	5.1	1.7

As seen in Table 30, the amplitude of the regulation value is greater in epileptics, too, after administration of salyrgan than after intake of water; and the variations of the regulation values show similar features here as in the control patients. There is first a rise and then a fall, so that at 15 o'clock, as a rule, the value is considerably lower than the initial value at 9 o'clock. At 15 o'clock the values for all the epileptics except for two are so low that they are within the normal limit. It is to be mentioned that these low regulation values after salyrgan

stay at a low level for a considerable length of time. Thus, at 7 o'clock in the morning after the experiment the average ammonia regulation value for the first group of epileptics was 4.6, for the second group 5.1, *i.e.*, the same values as observed at 15 o'clock on the day of the experiment. This means that the hyperammoniuria present in epileptics is reduced to a normal ammonia output after administration of salyrgan.

The variations of the regulation values during and after salyrgan diuresis are presumably to be explained in the following way: The increase in the diuresis will be accompanied by an increased output of Na and Cl in fairly equivalent amounts—as pointed out before. At the same time, however, there will also be an increase in the output of other strong acid radicals—*e.g.*, sulphates and organic acids—requiring alkalies or ammonia for their excretion, and this will produce a shift in the proportion between Na and the acid radicals in the direction of a preponderance of the acid elements, resulting in an increased ammonia production. This increased excretion subsides within 2-3 hours, however, and is then followed by an abnormally small excretion of acid radicals, on which account the ammonia production is lowered.

Still, as mentioned already, in order to prove conclusively that the hyperammoniuria is due to these conditions, all the acid and basic elements excreted with the urine would have to be determined quantitatively. But, at any rate, it may be considered established that there is a definite connection between hyperammoniuria and the excretion of water and salts.

In view of the above experiments, it seemed desirable to investigate the effect from continual administration of a diuretic upon the ammonia production in patients with hyperammoniuria. For this purpose I have employed tablets of theobromine sodium salicylate in a dosage of 1 g. $\times$ 3 daily for periods of 2-3 weeks alternating with periods in which the patients were not given any medicament.

This series comprises altogether 4 epileptics with hyperammoniuria. One of the patients was examined through a period of 4 months. The diuretic was found not to be able to abolish

the hyperammoniuria, as the regulation values kept essentially at the same average level in the periods with the remedy and in the periods of no medication. On the other hand, the curve was more stable in the periods of diuretic medication. In addition to the ammonia regulation values as expressions for the relative ammonia excretion, I also determined the ratio between ammonia and titrable acids. In previous investigations I have demonstrated that epileptics present a shift in this ratio, too—the preponderance of ammonia—but this ratio is more labile than the ammonia regulation value. This observation was further confirmed by the present experiments. Not only was the stability of the excretion from day to day greater in the periods when the patient received diuretin but the NH_3/acid ratio was on an average lower in this period. In the remaining three patients the findings were essentially the same as in this patient. In one, however, there was not only a fall in the NH_3/acid ratio, but also a distinct fall in the ammonia regulation value. This fall persisted for some days after the discontinuance of the medication, and then there was again a rise to the original level. The frequency of the seizures in the patients did not appear with certainty to be influenced by the treatment with diuretin—which is in keeping with the findings reported by Stubbe Teglbjærg.

The findings in this experiment are presumably to be explained in this way, that the constant influence of diuretin prevents—or, at any rate, counteracts—the periodical tendency to retention in the patients; but, in addition, it gives rise to a constant scarcity of salts in the organism so that more ammonia has to be produced continually than is required normally. The discontinuance of the remedy is followed by very wide variations in the ammonia production, and this is quite in concordance with the fact that only small salt reserves are at the disposal of the organism for the acid neutralization.

The present studies on the water and salt metabolism in epilepsy have shown unquestionably the presence of pathological conditions in this respect that may be recapitulated as follows:

1. Studies on the Na, K and Ca contents of the serum show essentially normal conditions, though with a tendency to low values. Not infrequently the obtained values are lower than the lowest value in the control material.
2. Studies on the Na and Cl content of the serum under the influence of theophyllin show, as a rule, a moderate fall, and this fall is greater in patients in the convulsive phase.
3. Studies on the excretion of water and Na after intake of one liter of water in patients with normo- and hyperammoniuria show in the hyperammoniurics on an average a smaller excretion of water in 4 hours and, in a higher degree, of Na.
4. Studies on the excretion of water, Na and Cl after injection of salyrgan in normo- and hyperammoniurics show a greater instability of the excretion in epileptics, and as the epileptic material may be divided into two groups, one with a smaller excretion of water, Na and Cl than observed in the normal material, the other with a larger excretion. All the patients with a small excretion present another abnormality: instead of falling—as is normal under the influence of salyrgan—the hydrogen ion concentration of the urine increases often to an excessive height (over 8).
5. Studies on the excretion of water, Na and Cl after intake of theophyllin confirm the observation of Yde: that the usual effect of theophyllin is sometimes absent in epileptics. In such cases there is an abnormally great fall in serum Na and serum Cl; but the Na and the Cl concentrations in the serum are not always parallel. The same applies to the excretion of the Na and Cl in the urine.
6. In patients adjusted on a water and salt equilibrium the Cl/Na ratio is fairly constant for morning urines, averaging about 1.26. In epileptics this ratio, on an average, is noticeably higher—namely, 1.55—which is due to the circumstance that particularly high values for these elements are more frequent in epileptics. The Cl/Na ratio falls after the administration of diuretics, and rises after injection of pitresin, in this way: in retention phases the Cl output is relatively greater than the Na excretion, while after administration

of diuretics the Na output is relatively greater than the Cl excretion. So, the increased Cl/Na ratio in epileptics is presumably to be interpreted as a tendency to retention.

Even though the individual experimental series are short and hence not positively decisive when considered separately, it seems to me that, taken together, they allow of the conclusion that the water and salt metabolism is relatively unstable, as is evident from a periodical decrease in the excretion of water and salts and a corresponding periodical increase in the excretion. Simultaneous examination of the concentrations in the blood and urine suggest that this abnormality at any rate is not due exclusively to abnormal conditions in the kidney, but also to abnormal conditions in the tissue depots, the latter retaining water and salts periodically with abnormal tenacity. Presumably these periods are of rather short duration, and for this reason, as shown by Stubbe Teglbjærg, no great variations can be demonstrated in the weight of the patients.

The mentioned disturbances appear to be of pathogenetic significance to the mechanism of the convulsive attacks. Various authors have shown that restriction of the water intake lowers the preparedness for convulsions, whereas excessive water intake + injection of pitressin increases this preparedness (McQuarrie, Stubbe Teglbjærg). In the present studies, the preparoxysmal period is found to be associated with a marked fall in serum Na and a lesser fall in serum Cl after administration of theophyllin. Presumably the pathogenetic significance of these changes to the convulsive attack is to be found in the colloid-osmotic conditions which also bring about the other abnormalities, resulting periodically in a "cellular oedema of the brain" that lowers the threshold for convulsions.

The mentioned disturbances in the water and salt metabolism appear to be in causal connection with an increased ammonia output, and it is rather probable that the hyperammonia is a result of the instability in the excretion of the solid alkalies. The ammonia output is found to be smallest in the normal subjects and greatest in those epileptics who are in the retention phase. Under the influence of salyrgan, the regulation

value is found to vary distinctly in normal subjects as well as in hyperammoniuric epileptics, the amplitude increasing to twice its normal range. This can be explained as attributable to the excretory ratios of acids and bases.

In the present studies most of the examined patients with hyperammoniuria were epileptics. In some of the experiments, however, also other patients with hyperammoniuria have been employed, and they presented quite the same disturbances in the water and salt metabolism as were found in the epileptics. In a previous work I have demonstrated that hyperammoniuria is no infrequent phenomenon in schizophrenics. In his extensive studies on the excretory conditions of schizophrenics, Gjessing has demonstrated that the psychic phases are associated with retention or a greatly increased output of nitrogen, water, and sodium chloride. In some of his experiments, Gjessing determined the ammonia N and pH, besides the total N, so that the regulation values could be calculated. Such calculation shows that the retention phases are associated with hyperammoniuria, the other phases with a normal ammonia output. This might be taken to indicate that in schizophrenics we meet with a similar biological abnormality as in the epileptics. These analyses are too few, however, to allow of any decisive conclusion, but it appears not to be quite the same abnormality, the phases being more protracted in the schizophrenics. In epileptics, for instance, the ammonia output may show diurnal variations from normal to greatly increased values—nay, such variations may take place even from hour to hour—whereas in schizophrenics the different phases last from 8 to 14 days. Further studies are required for elucidation of this question.

IV. ON THE CAUSE OF HYPERAMMONIURIA AND DISTURBANCES IN THE WATER AND SALT METABOLISM IN EPILEPSY

In looking for the cause of the disturbances in the water and salt metabolism demonstrated in epileptics, in particular two

possibilities have to be considered: 1) damage to, or functional disturbances in, the cerebral centers for regulation of the water and salt metabolism, or 2) hormonal disturbances.

It is well known that several endocrine glands exert some influence on the water and electrolyte equilibrium (the parathyroids, thyroid, hypophysis and suprarenals). Previously the attention was focussed especially on the parathyroids, but even though some authors still hold that certain forms of epilepsy are due to lesions of these glands, in recent years the interest has centered on the hypophysis. Altenberger & Stern were unable in 40 out of 79 epileptics of varying genesis to demonstrate any posterior pituitary hormone in the cerebrospinal fluid, whereas this hormone was absent only in 9 out of 80 non-epileptics, and most of these 9 patients were encephalitics or syphilitics.

Also Hendriksen assumes a deficiency of pituitary hormone in epileptics. He thinks that this hormone regulates the tonus of the capillaries (which has been demonstrated by Krogh to be the case in frogs) so that its absence causes an abnormal lability of the capillary tonus. Furthermore, one of the most characteristic symptoms of posterior pituitary deficiency consists in disturbances in the water metabolism, as it gives rise to diabetes insipidus. The disturbances demonstrated in epileptics do not correspond to this picture, however, and hence, at any rate, they cannot be due to complete absence of this hormone. But, the hormone production is governed cerebrally, as, for instance, lesions in the hypothalamus have been proved to produce diabetes insipidus, and the same applies to division of the infundebulum of the hypophysis. It is conceivable, therefore, that the disturbances in the water and salt metabolism might be due to a hypothalamic affection that gives a periodical decrease in the hormonal production of the posterior pituitary. A reduction in the amount of circulating posterior pituitary hormone gives rise to an increased reabsorption of Cl (and Na) in the renal tubules, and this is quite in concordance with the demonstration of the periodical decrease in the Cl and Na excretion by way of the kidneys. Still, it seems to me that the demonstrated disturbances in the water and salt metabolism are suggestive of ab-

normalities in the exchange of water and salts between the blood and tissues, rather than of abnormalities of the kidney function, and hence it seems very doubtful that this effect may be exerted through the posterior pituitary hormone. Finally, pitressin + excessive intake of water has a pronounced convulsion-eliciting effect, and this goes against the hypothesis of the attack being preceded by a posterior pituitary hormone deficiency in the blood.

On the other hand, Krogh has advanced a hypothesis about the presence of a permeability-regulating hormone in the blood stream. Whether this hormone comes from one of the known glands of internal secretion or is derived from some other source, is not known. But, if such a hormone exists, it seems to be a foregone conclusion that insufficiency of this hormone is the cause of the demonstrated disturbances. Already Georgi has advanced the assumption of changes in permeability as the cause of the biochemical changes in epileptics, and this assumption has further been corroborated by the findings of McQuarrie and collaborators in their studies on the behavior of the lipoids in epilepsy.

The theories about a causal connection between hormonal disturbances and epilepsy must yet be said to want a solid foundation. The difficulty in the elucidation of these problems is due in particular to the lack of a serviceable criterion of the metabolic anomalies mentioned. Nearly all the pathological findings in epilepsy are of a periodical nature and hence unsuitable to serve as a criterion of a state of insufficiency that possibly may be abolished by the administration of the active hormone. As emphasized previously, however, one of the demonstrated disturbances makes in some degree an exception to this rule, namely: hyperammoniuria. The ammonia output is not only subject to variation like the various other elements in the urine, but on an average it is increased, so that if it be possible by administration of a hormone or some other substance to lower the ammonia output to the normal level, we shall have gained a basis for further studies on the influence of this hormone upon the various biochemical anomalies.

Bisgaard and collaborators have investigated the influence of parathyroid preparations on the disturbances in the ammonia metabolism (*dysregulatio ammoniaci*) occurring in epileptics. Administration of parathyroid was found to be followed by a tendency to smaller variations in the ammonia excretion, though not constantly, and at any rate the regulation curve remained at the high level. As shown by Jørgen Madsen, it was often necessary, besides the hormone, to give CaCl_2 in order to obtain any effect on the ammonia output. It is a question, therefore, whether the effect observed may not have been entirely diuretic effect, as parathyroid and CaCl_2 have diuretic action (McCann, Hueper). For the curves obtained in the parathyroid-treated epileptics show a great resemblance to the curves obtained on administration of diuretics.

It is not very likely, I think, that any of the aforementioned known hormones are associated with the disturbances concerned here, as the characteristic symptoms of insufficiency in these hormones are not encountered in epileptics with hyperammoniuria. It seems more probable that these disturbances may involve the aforementioned permeability-regulating principle in the blood. To investigate this question will imply certain difficulties, as this principle is still rather obscure and cannot be isolated. One might conceivably try ingestion of blood, but it would undoubtedly prove impossible to make the patients ingest any sufficient amount of pure blood; and if the blood were prepared in some particular way—for instance, boiling—it is not very likely that the hormone would remain active. If this hypothetical active principle be present in the blood, however, it will also be present in the various organs rich in blood—among others, the liver—and as there are available some excellent liver preparations which we know contain a number of biologically active substances (antianemic principle, various vitamins) it will be natural in the first experiments to see whether liver preparations have any influence on the metabolic disturbances here concerned.

Such experiments have been carried out on some hyperammoniuric epileptics. Four of them will be described in the following.

*a. Effect of Liver Therapy on the Ammonia Excretion.
Protocols.*

Patient No. 1 (El. L.).

Date	Diuresis	mg.N in 2 cc.	NH ₃ N in 5 cc.	NH ₃ val.	pH	α	NH ₃ / acid	Remarks
1/9	1010	12.3	8.0	7.28	6.15	6.1	1.53	1 attack at
2/9	575++	14.8	9.2	7.00	6.30	6.1	1.52	7 o'clock
3/9	1600	10.0	5.2	5.88	6.50	5.8	1.53	
4/9	1490	11.6	6.2	5.83	6.30	5.5	1.51	
5/9	950	17.2	10.8	7.03	6.15	5.9	1.48	Rx. Exhepa
7/9	990	19.3	7.2	4.17	6.50	4.9	1.38	2 tubes $\times$ 2
8/9	1380	13.8	6.9	5.64	6.45	5.6	1.35	
9/9	1375	16.0	8.8	6.12	6.30	5.7	1.43	
10/9	1400	12.0	5.8	5.60	6.45	5.6	1.48	
11/9	1190	12.2	7.8	7.06	6.00	5.6	1.34	
12/9	1220	15.2	7.6	5.60	6.40	5.5	1.26	
14/9	1020	18.8	15.0	8.90	5.85	6.1	1.43	
15/9	995	16.0	10.8	7.52	6.00	5.8	1.47	
16/9	990	25.9	10.8	4.69	6.55	5.2	1.42	Discont. Exhepa
17/9	850	20.3	10.5	5.82	6.50	5.8	1.64	
18/9	1120	21.6	9.0	4.71	6.65	5.4	1.72	
19/9	810	22.7	14.2	7.03	6.30	6.1	1.49	
21/9	1090	20.8	13.5	7.24	6.15	5.9	1.58	
22/9	950	14.8	12.0	9.08	6.15	6.7	1.57	
23/9	1085	18.5	10.5	6.38	6.30	5.8	1.64	
24/9	1030	24.0	13.9	6.47	6.00	5.4	1.49	
25/9	1065	11.2	7.0	7.05	6.35	6.2	1.73	
26/9	1145	17.2	7.0	4.53	6.80	5.4	1.80	
28/9	870	22.0	15.3	7.81	5.75	5.5	1.57	

The average values before, during and after the treatment with Exhapa are:

	NH ₃ value	pH	α	NH ₃ /acid
Before	6.60	6.30	5.8	1.51
During	6.14	6.28	5.5	1.39
After	6.61	6.29	5.8	1.62

It will be noticed that the pH average is constant, while the NH_3 value is a little lower under the liver treatment, so that α becomes a little lower, too, though without reaching a normal level. Also the NH_3/acid ratio is lower under the treatment, but still moderately increased.

Patient No. 2 (O. L.).

Date	Diuresis	pH	NH_3	α	NH_3/acid	Remarks
1/9					2.04	
2/9	1030	6.35	8.41	6.7	2.20	
3/9	1065	5.85	9.81	6.4	1.85	
4/9	800+	6.40	6.48	6.0	1.94	
5/9	920+	6.45	9.63	7.4	2.25	
	954+	6.26	8.58	6.6	2.05	Rx. Exhepa 2 tubes $\times$ 2
7/9	1295	6.75	7.42	6.9	2.41	
8/9	985	6.25	8.27	6.5	1.38	
9/9	770	5.85	7.52	5.6	1.26	
10/9	1120+	5.85	7.97	5.7	1.42	
11/9	750+	6.35	6.35	5.8	1.51	
12/9	1160	5.75	9.65	6.1	1.82	
14/9	920+	6.30	5.84	5.5	1.88	
15/9	1080	6.00	6.46	5.4	1.63	
	1010	6.14	7.43	5.9	1.66	Discont. Exhepa
16/9	970	6.20	6.80	5.8	2.20	Rx. Ventriculin 20 g.
17/9	910+	6.30	6.29	5.7	1.95	
18/9	1090	6.50	5.80	5.8	2.44	
19/9	1050	6.60	5.73	5.9	2.23	
21/9	625	5.65	7.18	5.1	1.90	
22/9	1490	6.45	4.39	5.0	2.32	
23/9	1305	5.90	7.58	5.7	2.29	
24/9	1010	5.80	8.98	6.0	2.13	
25/9	1160	5.65	9.48	5.9	2.32	
26/9	1100	6.30	7.97	6.5	2.32	
28/9	1690	6.15	6.89	5.8	1.76	
29/9	2100	6.50	6.13	5.9	1.98	
30/9	1855	6.15	6.70	5.7	2.10	
1/10	1325	6.30	5.48	5.4	1.72	
2/10	900+	6.00	6.54	5.4	1.91	
3/10	900	6.00	9.06	6.4	1.88	

(Pt. No. 2, cont.)

Date	Diuresis	pH	NH ₃	α	NH ₃ /acid	Remarks
5/10	1650	6.15	5.62	5.2	1.78	
6/10	1130+	6.35	5.98	5.7	2.35	
7/10	1715	5.65	7.70	5.3	1.87	
8/10	1250	6.15	7.52	6.1	1.91	
	1261	6.13	6.89	5.7	2.07	Discont. Ventriculin.
9/10	565+	6.55	4.95	5.4	1.62	
10/10	1025+	6.95	4.14	5.3	2.08	
12/10		5.45	7.17	4.7	1.14	
13/10	1050	5.90	5.74	4.9	1.41	
14/10	825	6.95	4.35	5.5	3.05	
15/10	725+	6.50	10.11	7.6	2.80	
16/10	490+	5.70	7.23	5.2	1.92	
17/10	800+	5.65	8.10	5.4	1.88	
19/10	1105+	5.85	5.51	4.8	1.83	
20/10	1230	5.65	8.78	5.6	1.83	
21/10	1310+	6.70	4.80	5.5	2.42	
	912	6.17	6.44	5.4	2.00	Rx. Ultranol
22/10	1170	5.70	9.72	6.0	1.91	
23/10	560+	6.65	4.96	5.5	1.68	
24/10	750	5.70	8.45	5.6	1.84	
26/10	1075	6.70	5.62	5.9	1.93	
27/10	960+	6.50	5.41	5.6	2.26	
28/10	1105	6.65	6.38	6.3	2.45	
29/10	990	7.35	3.19	5.0	2.85	
30/10	935+	6.55	6.54	6.2	2.01	
31/10	600+	6.45	8.21	6.8	2.13	
2/11	1260	6.30	6.22	5.7	1.98	
3/11		5.95	7.50	5.8	1.83	
4/11	1165	6.70	5.52	5.9	2.53	
	961	6.43	6.48	5.9	2.12	Discont. Ultranol
5/11	810	6.26	7.38	6.1	1.82	
6/11	840+	6.10	11.42	7.4	2.36	
7/11	415+	5.55	12.14	6.4	1.56	
8/11	1090	6.6	5.64	5.8	2.27	
10/11	820	6.80	4.19	5.2	2.65	
11/10	1125	6.25	4.83	5.0	1.84	
	850	6.25	7.60	6.0	2.08	

(Pt. No. 2, cont.)

Date	Diuresis	pH	NH ₃	α	NH ₃ /acid	Remarks
18/2					2.20	
20/2					1.70	
21/2					2.50	
28/2					3.22	
5/3					2.60	
6/3					1.94	
					2.36	Rx. Exhepa 2 tubes $\times$ 2
7/3					1.84	
9/3					1.80	
10/3					1.44	
11/3					1.56	
12/3					1.56	
13/3					1.80	
14/3					1.50	
16/3					2.00	
17/3					1.50	
18/3					1.60	
19/3					1.40	
20/3					1.80	
21/3					1.54	
31/3					1.48	
					1.63	Cont. Exhepa. Rx. Diuretin
2/4					1.50	
3/4					1.38	
4/4					1.32	
6/4					1.82	
7/4					1.28	
8/4					1.28	
11/4					1.30	
14/4					1.20	
					1.38	Discont. Diuretin. Cont. Exhepa 1 tube. $\times$ 4
15/4					1.50	
16/4					1.34	
17/4					1.10	
18/4					1.18	
					1.28	Discont. Exhepa.

(Pt. No. 2, cont.)

Date	Diuretics	pH	NH ₃	α	NH ₃ /acid	Remarks
20/4					1.88	
21/4					1.94	
27/4					1.90	
28/4					2.62	
29/4					2.45	
30/4					2.74	
1/5					2.08	
2/5					2.38	
4/5					2.30	
5/5					2.10	
7/5					2.00	
9/5					1.98	
11/5					1.90	
13/5					2.00	
					2.15	Rx. Exhepa
14/5					1.90	
22/5					1.70	
26/5					2.04	
27/5					1.74	
28/5					1.40	
29/5					1.50	
30/5					1.55	
2/6					1.50	
3/6					1.55	
4/6					1.55	
6/6					1.60	
					1.64	Discont. Exhepa
8/6					1.98	
9/6					2.35	
10/6					1.56	
11/6					2.90	
12/6					1.94	
13/6					2.86	
					2.26	

We thus find:

Treatment	pH	NH ₃	α	NH ₃ /acid
No drug	6.26	8.58	6.6	2.05
Exhepa 2 tubes $\times$ 2	6.14	7.43	5.9	1.66
Ventriculin	6.13	6.89	5.7	2.07
No drug	6.17	6.44	5.4	2.00
Ultranol	6.43	6.48	5.9	2.12
No drug	6.25	7.60	6.0	2.08
" "				2.36
Exhepa 1 tube $\times$ 2				1.63
Exhepa + diuretin				1.38
Exhepa 1 tube $\times$ 4				1.28
No drug				2.15
Exhepa				1.64
No drug				2.26

So in all the periods in which the patient was given Exhepa there was a decrease in the NH₃/acid ratio. Administration of Exhepa also gave a fall in the ammonia regulation value, owing to a fall in the ammonia value, pH remaining constant. In contrast to the NH₃/acid ratio, the regulation value kept at a low level for a whole month after the discontinuance of Exhepa therapy.

Patient No. 3 (K. A. S.).

Date	Diuresis	pH	NH ₃	α	NH ₃ /acid	Remarks
1/9					1.93	
2/9	1425	6.10	10.34	7.0	1.78	
3/9	2200	6.40	9.39	7.2	1.68	
4/9	1310	6.20	8.43	6.5	1.54	
5/9	1450	6.30	8.32	6.6	1.72	
	1564	6.25	9.12	6.8	1.73	Rx. Exhepa 2 tubes + 2
7/9	1590	6.30	8.34	6.6	1.26	
8/9	2460	6.0	9.67	6.6	1.52	
9/9	2165	5.90	9.73	6.4	1.64	
10/9	1990	6.30	9.60	7.1	1.67	
11/9	2220	5.85	11.67	6.9	1.57	

(Pt. No. 3, cont.)

Date	Diuresis	pH	NH ₃	α	NH ₃ /acid	Remarks
12/9	2095	5.75	11.00	6.5	1.60	
14/9	2010	5.85	10.03	6.4	1.61	
15/9	1820	6.35	6.95	6.1	1.58	
16/9		5.55	9.08	5.5	1.24	
	2044	6.00	9.56	6.2	1.52	Discont. Exhepa
17/9		5.95	6.37	5.3	1.12	
18/9		6.45	8.62	7.0	1.78	
19/9		6.55	8.58	7.1	1.62	
21/9		5.90	10.37	6.6	1.55	
22/9		6.25	8.29	6.5	1.44	
23/9		6.55	5.72	5.8	1.59	
24/9		6.35	4.23	4.8	1.62	
25/9		5.65	9.61	5.9	1.57	
26/9		7.00	6.34	6.7	1.70	
28/9		6.00	6.82	5.5	1.52	
29/9		5.60	9.80	5.9	1.42	
30/9		5.85	8.52	5.9	1.69	
1/10		5.85	11.24	6.8	1.88	
2/10		5.85	9.92	6.4	1.69	
3/10		6.30	8.47	6.7	1.61	
5/10		5.70	9.16	5.9	1.73	
6/10		6.30	7.89	6.4	1.79	
7/10		6.10	9.24	6.6	1.90	
8/10		6.15	8.36	6.4	1.75	
		6.13	8.34	6.3	1.63	Rx. Exhepa 2 tubes $\times$ 2
9/10		6.30	7.31	6.2	1.53	
10/10		6.45	7.46	6.5	1.61	
12/10		5.80	9.27	6.1	1.42	
13/10		6.05	10.01	6.8	1.78	
14/10		6.25	8.00	6.4	1.42	
15/10		6.20	6.71	5.8	1.16	
16/10		6.15	8.98	6.6	1.65	
17/10		6.70	6.53	6.3	1.44	
19/10		6.45	7.41	6.5	1.73	
20/10		6.90	5.47	6.1	2.01	
21/10		6.10	8.71	6.4	1.58	
		6.30	7.81	6.3	1.57	Discont. Exhepa

(Pt. No. 3, cont.)

Date	Diuresis	pH	NH ₃	α	NH ₃ /acid	Remarks
8/2					1.26	
10/2					1.95	
11/2					1.75	
12/2					1.60	
13/2					1.58	
14/2					1.95	
15/2					1.88	
					1.71	Rx. Exhepa
17/2					1.72	
18/2					1.45	
19/2					1.50	
20/2					1.42	
21/2					1.54	
22/2					1.60	
24/2					1.66	
25/2					1.50	
26/2					1.56	
27/2					1.60	
					1.55	
28/2					1.48	Cont. Exhepa. Rx. Diuretin.
29/2					1.26	
2/3					1.86	
3/3					1.45	
4/3					1.26	
5/3					1.90	
6/3					1.68	
7/3					1.18	
9/3					1.12	
					1.47	Cont. Exhepa. Discont. Diuretin.
10/3					1.15	
11/3					1.66	
12/3					1.46	
13/3					1.48	
14/3					1.18	
16/3					1.68	

(Pt. No. 3, cont.)

Date	Diuresis	pH	NH ₃	α	NH ₃ /acid	Remarks
17/3					1.78	
18/3					1.74	
					1.52	Discont. Exhepa
19/3					1.58	
20/3					1.64	
21/3					1.48	
23/3					1.76	
24/3					1.28	
25/3					1.84	
26/3					1.72	
27/3					1.48	
28/3					1.90	
					1.63	

We thus find:

Treatment	pH	NH ₃	α	NH ₃ /acid
No drug	6.25	9.12	6.8	1.73
Exhepa 2 tubes $\times$ 2	6.00	9.56	6.2	1.52
No drug	6.13	8.34	6.3	1.63
Exhepa 2 tubes $\times$ 2	6.30	7.81	6.3	1.57
No drug				1.71
Exhepa				1.55
Exhepa + diuretin				1.47
Exhepa				1.52
No drug				1.63

Patient No. 4 (J. L. P.).

Date	Diuresis	pH	NH ₃	α	NH ₃ /acid	Remarks
5/1				5.6	1.48	No drug
6/1				6.0	1.50	
7/1				6.0	1.64	
8/8				6.0	2.04	
9/1				6.1	1.72	

(Pt. No. 4, cont.)

Date	Diuresis	pH	NH ₃	α	NH ₃ /acld	Remarks
11/1				7.2	2.65	
12/1				6.4	1.90	
14/1				6.5	1.88	
15/1				6.4	2.10	
16/1				6.4	2.04	
19/1				7.0	1.94	
20/1				7.8	2.04	
21/1				8.0	1.94	
				6.6	1.76	
5/12				7.0	2.28	
6/12				6.9	1.94	
7/12				6.6	2.18	
				6.8	2.13	Rx. Exhepa 1 tube $\times$ 2
9/12				5.6	1.24	
10/12				5.7	1.14	
11/12				5.7	1.36	
12/12				5.7	1.22	
13/12				5.7	1.26	
14/12				5.8	1.30	
16/12				4.7	1.38	
17/12				5.6	1.54	
18/12				5.5	1.44	1 attack
19/12				5.7	1.68	1 attack
20/12				5.8	1.72	1 attack
21/12				5.9	1.50	
23/12				5.9	1.50	
27/12				5.1	1.16	
29/12				5.6	1.20	1 attack
30/12				6.6	1.52	4 attacks
31/12				6.0	1.41	2 attacks
2/1				5.0	1.51	
3/1				5.6	1.32	
4/1				6.0	1.34	
				5.7	1.38	Discont. Exhepa
1/9					1.43	1 attack
2/9	1370+	6.50	6.05	5.9	1.41	1 attack

(Pt. No. 4, cont.)

Date	Diuresis	pH	NH ₃	α	NH ₃ /acid	Remarks
3/9	2290	6.50	7.27	6.5	1.47	2 attacks
4/9	1565	5.9	6.36	5.2	1.45	2 attacks
	1741	6.30	6.56	5.9	1.44	Rx. Exhepa 2 tubes $\times$ 2
7/9	1000	6.15	5.20	5.0	1.04	
8/9	1340	6.30	6.21	5.7	1.14	
9/9	1900	5.70	6.42	4.9	1.05	
10/9	1880	5.95	5.54	4.9	0.95	
11/9	1560	5.85	5.44	4.7	0.98	
12/9	1970	6.20	4.56	4.8	0.83	2 attacks
14/9	1400	6.20	5.23	5.1	1.28	
15/9	1720	6.05	4.64	4.6	1.07	
16/9	1240	6.30	4.28	4.7	0.97	
	1557	6.07	5.28	4.9	1.03	Discont. Exhepa
17/9	1650	6.30	5.00	5.1	0.90	
18/9	1580	5.90	5.04	4.6	1.12	
19/9	1230	6.30	4.53	4.9	1.00	
21/9	1430	6.30	5.50	5.4	1.25	
22/9	2220	6.50	3.92	4.7	0.84	
23/9	1560	6.35	4.44	4.9	0.93	
24/9	1420	6.30	4.85	5.0	1.16	2 attacks
25/9	1610	6.10	4.98	4.9	1.09	1 attack
26/9	1950	6.50	4.01	4.8	0.99	3 attacks
28/9	1700	6.35	6.27	5.8	1.78	3 attacks
29/9	1800	6.50	6.53	6.1	1.75	1 attack
30/9	1280	6.35	6.01	5.7	1.39	
1/10	1700	5.90	5.72	4.9	1.30	
2/10	2130	6.15	7.20	5.9	1.26	
3/10	1400	5.90	6.17	5.1	1.12	
5/10	1250	6.10	5.14	4.9	0.99	
6/10	2470	6.25	3.71	4.4	0.93	
7/10	1630	6.10	5.33	5.0	0.83	
8/10	940	6.05	5.38	5.0	0.98	
9/10	1770	6.25	4.27	4.7	0.98	
10/10	1290	6.25	7.81	6.3	1.44	2 attacks
12/10	1320	6.40	5.51	5.5	1.12	1 attack
13/10	840	5.85	6.85	5.3	1.27	
14/10	2100	6.20	4.66	4.8	1.11	
15/10	810	5.90	5.71	4.9	1.08	

(Pt. No. 4, cont.)

Date	Diuresis	pH	NH ₃	α	NH ₃ /acid	Remarks
16/10	1790	5.90	6.10	5.1	1.23	
17/10	1280	6.25	5.75	5.4	1.26	
19/10	1170	6.05	5.22	4.9	1.29	
20/10	1450	6.35	6.03	5.7	1.27	
21/10	1670	6.05	5.72	5.1	1.03	1 attack
22/10	1570	6.45	6.05	5.8	1.16	4 attacks
	1549	6.20	5.43	5.2	1.16	Rx. Ultranol
23/10	2150	6.30	6.40	5.8	1.19	1 attack
24/10	1520	6.25	6.49	5.8	1.43	3 attacks
26/10	1230	6.30	4.01	4.6	1.07	
27/10	1880	6.50	5.88	5.8	1.38	1 attack
28/10	1445	6.05	7.14	5.7	1.51	1 attack
29/10	900	6.45	5.91	5.8	1.47	
30/10	1310	5.70	6.92	5.1	1.11	1 attack
31/10	1390	6.15	5.60	5.2	1.09	
2/11	1450	6.25	5.28	5.2	1.10	
3/11	1330	6.20	4.93	5.1	1.01	1 attack
4/11	1800	6.75	3.36	4.6	0.95	
	1491	6.26	5.63	5.3	1.21	

We thus find:

Treatment	pH	NH ₃	α	NH ₃ /acid
No drug			6.6	1.76
No drug			6.8	2.13
Exhepa 1 tube $\times$ 2			5.7	1.38
No drug	6.30	6.56	5.9	1.44
Exhepa 2 tubes $\times$ 2	6.07	5.28	4.9	1.03
No drug	6.20	5.43	5.2	1.16
Ultranol	6.26	5.63	5.3	1.21

Administration of Exhepa, 1 tube $\times$ 2, is followed by a considerable fall in the regulation value and in the NH₃/acid ratio. Discontinuance of this treatment is followed by a slight rise in the two values. When the treatment with Exhepa is

repeated there is again a fall in these two values, so that in this period they are within the normal limit. When this treatment is discontinued there is again a moderate increase in the two values, and this rise continues in the last period, when the patient is given ultranol, though without reaching the initial high levels.

As a rule, the convulsive periods are associated with a rise in both the ammonia regulation value and the NH_3/acid value.

b. *Discussion.*

The administration of Exhepa to these patients, then, is followed by such a constant fall in the ammonia excretion that it has to be considered most probable that this preparation contains a principle active in this respect. In Patient No. 4 who showed a pronounced hyperammonuria prior to the experiment, both the regulation value and the NH_3/acid ratio were lowered so markedly as to fall within the normal limits. This patient had been examined repeatedly before and had always shown a marked degree of hyperammoniuria.

In the experiments in which both the hydrogen ion concentration and the ammonia value are recorded, it will be noticed that it is in particular the ammonia value which is reduced under Exhepa treatment. But also pH is usually lowered somewhat. So this reduction cannot be a base effect, as, if this were the case, the reduction in the ammonia value would be accompanied by a rise in pH.

As to the mechanism in the lowering of the ammonia output, for the present it will have to be left an open question, as it was not practicable for me at the same time to examine the excretion of water and salts. No pronounced changes were ascertained in the amount of the diuresis under the Exhepa treatment, but as the patients had not been adjusted to a water or salt equilibrium during the experiments it would hardly have been possible to ascertain any variations of the diuresis. Observations have been reported, however, which indicate that liver preparations have a diuretic effect, and Føldes, employing liver

therapy as a means of dehydration in epilepsy and migraine, claims he obtained a favorable effect from the treatment in these lesions. As both parathyroid and thyroid preparations have a diuretic action, it seems reasonable to think that this is no specific effect of the hormones concerned, but rather an effect connection with the principle common to preparations of internal organs, and it seems appropriate, therefore, again to call attention to the aforementioned permeability-regulating hormone in the blood.

A short time ago, some studies on the permeability of the red blood cells were reported by O. Bang and S. Ørskov, showing that liver and stomach preparations are able to alter the permeability for various substances, *e.g.*, glucose. This effect asserts itself both in the case of normal permeability (Ørskov) and in the increased permeability encountered in pernicious anemia (Bang & Ørskov). The authors show that this effect is not dependent on the anemia, as the permeability is lowered before any changes appear in the blood picture. This effect persists for a relatively long time after discontinuance of the treatment—as is seen also in my experiments.

It seems to me that the findings of Bang & Ørskov, together with my experiments with administration of liver preparation, lend support to the assumption of changes in permeability as the possible cause of the disturbances in epilepsy demonstrated in the present work. Exhepa given in the doses here employed has not been able noticeably to lower the frequency of seizures in the patients, it is true, but in spite of the liver therapy the convulsive periods are accompanied by a rise in the ammonia output showing that the active principle in the liver preparations has not been able to check the marked preparoxysmal changes. Further, the effect of this treatment has differed somewhat in the various patients, and only in one case has it been possible to produce perfectly normal values for the regulation value and NH_3/acid ratio. It seems very likely, therefore, that the doses here employed contain the active principle only in amounts insufficient for our purpose.

The present studies thus lend support to the theories about

a reversible increase in the permeability with altered colloid-osmotic conditions of the tissue cells, which in the brain cells give rise to an increased irritability (Georgi, McQuarrie, Engel, Ziegler and others). At intervals, the increase in permeability will cause a mobilization of electrolytes (K, Na and Cl) from cells to the blood, wherefrom they are excreted with the urine, whereas water will be retained in the cells. Thus the retention period is characterized by retention of a greater or smaller amount of water, while the organism becomes more and more poor in electrolytes. When the state of swelling of the cells reaches a certain limit, an attack will be elicited, giving rise somehow to an alteration of the colloid-osmotic conditions with excretion of greater amounts of urine poor in salts.

It seems to me that my findings are explainable after this theory. It explains the periodical low electrolyte values in the blood and the periodically slight effect of diuretics on the excretion of water and salts. Owing to the osmotic conditions, the water is retained in the cells, and because of the lack of electrolytes, the excretion of Na and Cl will be slight, too. This also explains the great reduction in the electrolyte concentration of the blood in the preparoxysmal period. Furthermore, it also explains the fact that no less than 4 out of 12 epileptics had convulsive seizures after intake of theophyllin, as the reduction in the Na and Cl concentrations of the blood increases the "swelling" of the cells, and it is reasonable to assume that the mechanism in the convulsion-eliciting effect of excessive intake of water is of the same character.

The real underlying cause of these disturbances is still obscure. Even if we maintain the hypothesis concerning a permeability-regulating hormone, I think, in view of the periodicity of the demonstrated abnormalities, it will be most natural to think that the "hormone" is governed by the central nervous system—presumably from, or through, centers in the hypothalamus.

Even though these disturbances constitute an important link in the mechanism of the convulsions, they are undoubtedly not to be regarded as specific of the epilepsy. Similar disturbances

are found in patients who have no epileptic convulsions. But, whether the real cause is an affection of the hypothalamus or a constitutional peculiarity—a humoral anomaly of the constitution—it still is of great interest simply through the fact that it has to be considered a contributory cause of such a serious neuropsychiatric syndrome as the epileptic attack. So the possibility cannot be excluded—and to me it seems even very probable—that the mentioned changes in the brain cells may also otherwise give rise to cerebral symptoms, presumably, in particular, of psychiatric nature.

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BLOOD SUGAR AND CHOLESTEROL IN ELECTRIC SHOCK

BY

BORIS SILFVERSKIÖLD and SVEN STENBERG

In recent years the chemical changes in the blood following cardiazol and electric shock treatment have raised great interest. In a monograph on the problems Müller calls attention to the fact that the results of investigations often do not agree, *inter alia* because different investigators have made their tests shorter or longer time after the convulsion.

However, in regard to the reaction of the blood sugar after cardiazol shock, agreement seems to prevail. American, Swiss and Italian authors have shown that the blood sugar concentration increases after the attack and attains its maximum in about 30 minutes. Then there is a more or less slow decrease to pre-paroxysmal level. In Sweden Wohlfart has carried out similar investigations.

In regard to cholesterol, opinions differ. The Italians Brozzi, and Schiapatti (1937) as well as Zerbini (1938) have found "a very regular increase" in the cholesterol contents of the blood after the cardiazol shock. The Spaniards Cuatrecasas, Vita and Camoirano (1940) have examined 25 cases and found no increase in blood cholesterol after the attack.

After electric shock Wohlfart found in some cases an increase in the blood sugar, reaching its maximum 10—35 minutes after the attack. In one case a subsequent, comparatively long state of hyperglycemia was observed. Castellucci (1940), too, has shown the occurrence of hyperglycemia lasting 2—3 hours from

the electric shock. Further he has found that this may occur also after abortive attacks, *e.g.*, attacks without convulsions. Thus, according to this author, the blood sugar increase would not be a result of the muscular effort.

Cavagna (1939) has examined the blood cholesterol before and after the attack under electric shock treatment. He has found a small increase for about 70 per cent of the cases.

As all the above-mentioned works have been available to the authors only in abstracts we cannot discuss them but only report the statements.

Our intention has been only to investigate if the amounts of sugar and free cholesterol in the blood show any quantitative changes in connection with electric shock. Previously one of the authors (*Stenberg* 1941) has shown, that free and combined cholesterol agree in regard to their variations, so we have limited this investigation to free cholesterol. (Regarding the technique we refer to the above-mentioned work.) Of course it is not quite sure that the same holds true here. However, free cholesterol is easier to examine—an important point when we had to make three tests in immediate succession with duplicate determinations. Blood sugar determinations were made after Folin's micromethod.

TABLE 1.
Free cholesterol and blood sugar in electric shock with convulsion.

Name	No.	Sex	Diagnosis	Free chol. mg. per 100 cc.			Blood sugar		
				Before shock	Immediately after shock	1 hour after shock	Before shock	Immediately after shock	1 hour after shock
G.J.	58/41	♂	man.-depr.	42.65	56.25	45.66	0.095	0.116	0.135
				46.76	58.97	46.62	0.105	0.114	0.118
				47.65	61.84	52.57	0.115	0.146	0.121
A.S.	29/41	♂	schiz.	45.08	—	—	0.084	—	—
				53.82	65.66	53.24	0.090	0.104	0.093
				61.99	70.07	61.32	0.094	0.105	0.101
				58.60	69.11	62.35	0.092	0.105	0.102
S.F.	139/41	♂	man.-depr.	68.68	—	—	0.118	—	—
				91.25	97.94	88.09	0.115	0.124	0.146
				77.64	84.04	77.42	0.148	0.182	0.176

Name	No.	Sex	Diagnosis	Free chol. mg. per 100 cc.			Blood sugar		
				Before shock	Immediately after shock	1 hour after shock	Before shock	Immediately after shock	1 hour after shock
O.Ö.	124/41	♀	man.-depr.	47.94	—	—	0.133	—	—
				78.38	—	—	0.120	—	—
B.L.	135/41	♂	man.-depr.	66.39	70.81	70.51	0.109	0.114	0.106
				70.14	86.02	70.14	0.100	0.115	0.111
K.P.	1/41	♂	man.-depr.	83.31	96.24	85.88	0.112	0.123	0.141
				87.79	96.61	91.47	0.101	0.131	0.130
				—	100.73	92.05	0.120	0.137	0.120
E.M.P.	210/41	♀	schiz.	79.11	89.63	85.58	0.106	0.123	0.149
				81.25	89.48	85.59	0.102	0.124	0.130
				93.23	104.12	96.76	0.100	0.128	0.123
A.P.	287/41	♀	man.-depr.	84.78	—	—	0.113	—	—
				68.60	71.91	68.31	0.117	0.135	0.192
				78.01	89.85	81.69	0.116	0.120	0.147
O.Ö.	124/41	♀	man.-depr.	104.34	110.58	102.20	0.098	0.110	0.106
				98.01	98.82	98.89	0.123	0.136	0.165
D.L.	382/41	♂	man.-depr.	83.52	94.26	78.38	0.114	0.127	0.151
E.M.P.	210/41	♀	schiz.	95.07	103.97	95.14	0.114	0.126	0.132
K.J.	292/41	♂	schiz.	69.70	75.88	91.02	0.097	0.107	0.099
K.H.	39/41	♀	man.-depr.	73.67	82.79	71.91	0.112	0.127	0.120
M.W.	57/41	♂	man.-depr.	94.26	104.99	93.82	0.094	0.104	0.105
H.A.	353/41	♀	man.-depr.	103.82	112.20	100.88	0.100	0.117	0.103
D.N.	338/41	♀	man.-depr.	79.85	88.38	74.55	0.092	0.090	0.087
T.L.	301/41	♂	schiz.	57.64	63.97	55.00	0.094	0.095	0.095
D.T.	327/41	♀	man.-depr.	80.88	82.20	75.88	0.105	0.138	0.148
G.G.	556/41	♀	man.-depr.	59.41	67.50	65.73	0.081	0.110	0.105
H.G.	416/41	♀	psychogen. depr.	71.47	78.38	72.79	0.096	0.161	0.109
G.B.	432/41	♀	man.-depr.	57.20	65.00	55.73	0.093	0.098	0.100
K.K.	367/41	♀	psycho- pathic	58.23	62.35	58.97	0.078	0.089	0.078
K.N.	394/41	♂	man.-depr.	50.14	53.38	51.47	0.070	0.078	0.082
B.E.	440/41	♀	psycho- pathic	69.41	81.61	71.32	0.084	0.100	0.100
A.L.	322/41	♀	schiz.	54.85	64.85	57.94	0.074	0.094	0.083
I. L.	379/41	♀	man.-depr.	68.08	75.00	67.20	0.111	0.122	0.118

The calculations are found in Table 2.

As will be seen from Table 1, the patients comprised at our first examination melancholiacs, maniacs, schizophrenics and

psychopaths. The tests were made about 10 o'clock a.m. and the patients received no food before that time. For reasons pointed out by *Silfverskiöld* (1941) the patients were given oxygen inhalation before the electric shock. In that way general asphyxia was avoided, which was important as the cholesterol and the blood sugar otherwise might have been influenced by asphyxial convulsion. The first test was made immediately before the patient was taken to the treatment room. About 90 seconds later the second test was made. Then the convulsion was all over and the patients were in a calm state. The third test was made an hour later.

Table 1 shows, that in all cases, irrespective of the diagnosis, and whether the patients had had attacks earlier or not, we found a statistically significant increase in blood sugar as well as in cholesterol immediately after the attack. After one hour the cholesterol was on the same level as before the convulsion, whereas the blood sugar had not yet got down to its initial level. The positive correlation between cholesterol and blood sugar in these cases is very interesting.

As opinions diverged to some extent regarding the cholesterol in the blood immediately after a cardiazol convulsion we decided to try to investigate the problem. (On account of technical difficulties we did not examine the cholesterol one hour after the cardiazol convulsions.)

According to earlier investigations the variations in regard to blood sugar are unambiguous. It will be seen from Table 2, that a statistically significant increase in cholesterol is found also after a cardiazol convulsion. There is hardly any reason to assume that the cholesterol would not decrease one hour after a cardiazol convulsion in the same way as after electric shock.

Thus the cardiazol shock and the electric shock both bring about unconsciousness followed by tonic-clonic convulsions and a temporary increase in the amounts of sugar and free cholesterol in the blood.

To get closer to the problem we started from the question whether the chemical changes in the blood are correlated with the convulsion or whether they occur also in response to smaller

repeated doses, which are not followed by convulsion. *Wohlfart* (1941) has carried out such studies in regard to cardiazol shock. After injections not followed by convulsion he found in 2 cases an initial decrease in blood sugar, which, however, soon passed. In a third case there was a small increase of short duration immediately after the injection. *Wohlfart* has told us that he also injected aqua destillata on patients who expected to have cardiazol convulsion; also then he could ascertain an increase in blood sugar. *Wohlfart* thinks that in these cases it is a question of an emotional hyperglycemia ad modum Cannon, which seems reasonable. Faced by the prospect of a cardiazol shock patients generally are very anxious.

TABLE 2.
 $M \pm \varepsilon(M) = \text{Mean} \pm \text{Standard error}$

		Diff. before — immediately after convuls.			Diff. before — 1 hour after convuls.		
	Number of cases	$M \pm \varepsilon(M)$		σ	$M \pm \varepsilon(M)$		σ
<i>El. shock with convuls.</i>							
Cholesterol	24 ¹⁾	— 9.06	± 0.88	± 4.32	— 1.95	± 1.30	± 6.38
Blood sugar	24	— 0.016	± 0.0027	± 0.0133	— 0.016	± 0.0030	± 0.0148
<i>Cardiazol convuls.</i>							
Cholesterol	15	— 5.95	± 1.57	± 6.09			
<i>El. shock without convuls.</i>							
Cholesterol	15	— 0.93	± 1.25	± 4.86			
Blood sugar	15	— 0.0032	± 0.0039	± 0.0150			
<i>Valsalva's experiment</i>							
Cholesterol	9	— 6.06	± 3.33	± 9.99			
Blood sugar	9	— 0.0034	± 0.0042	± 0.0125			
<i>Muscular work</i>							
Cholesterol	8	— 1.69	± 0.77	± 2.17			

¹⁾ Table 1 includes 41 determinations on 24 patients.

Before electric shock patients show no signs of anxiety as a rule. It could therefore be decided if the chemical changes in the blood are correlated with convulsions. In this investigation

we gave the patient a "shock" strong enough to make him unconscious but too feeble to cause a convulsion. The figures for blood sugar as well as those for cholesterol varied both upwards and downwards, but, as appears from Table 2, no statistically significant variation in the one or the other direction could be established. It is interesting to compare these observations with those made by *Hammargren* and *Stenberg* (1942) in an investigation of the results of electric shock treatment with and without convulsion. Cases treated with shock causing unconsciousness but no convulsion did not show any statistically significant changes either in regard to recovery or to other changes in their condition.

As shown by *Silfverskiöld* and collaborators there is a certain agreement between electric convulsion and Valsalva's experiment. In both cases a rise in the thoracic and abdominal pressures is found as well as in the arterial, venous and liquor pressures. As these increased pressures might influence the blood sugar and cholesterol, a series of Valsalva's experiments was carried out. The experimental persons were directed to blow against a manometer for 30 seconds. Asphyxia was avoided by deep breathing for a few seconds before the experiment. Of course the increase in pressure obtained in such experiments is not so strong as that observed in electric convulsion. Table 2 shows that in the experimental persons the blood sugar as well as the cholesterol varied to a great extent. It was not possible to establish a statistically significant difference in either direction.

Our investigation having advanced so far, the question arose, whether the ascertained chemical changes in the blood have a direct connection with the cerebral processes, or whether they should be regarded as phenomena correlated with muscular efforts. In order to elucidate this question some experiments were carried out. Healthy persons were told to do strong muscular movements (e.g. raising a weight of 35 kilos above the head and bringing it down to the floor again 2 times in 30—40 seconds). As will be seen from Table 2, there is a small rise in cholesterol, but this is not as regular as the increase showed in Table 1 and

not statistically significant. Yet it should be emphasized that the exertion at lifting of weights hardly can be as great as the muscular strain at the intensive tonic-clonic convulsion of the shocks. Thus it cannot be definitely excluded that a certain increase in blood sugar and cholesterol may possibly arise from the short, violent muscular effort. According to earlier investigations (*Patterson 1927; Stenberg 1929; Gaddie and Dunlop 1931*), however, the cholesterol does not seem to be influenced by moderate muscular work. As the average difference arising from muscular work is much smaller than the difference appearing in connection with the treatment it does not seem probable that the increase in cholesterol during the treatment is due to the muscular efforts. However, only a few experiments with muscular movements were made. It would have been desirable to have more persons available for the experiments. Therefore it cannot be definitely excluded that in a greater material the muscular exertion might prove to play a rôle. The values obtained are of such a character as to exclude the possibility of an equally great change from the muscular work carried out as that brought about by the electric shock. Considering that other authors have obtained negative results, it does not seem very probable that the cholesterol increase after the convulsions would be due to muscular exertion as is the case with the sugar increase. As the electric convulsion means a greater exertion, however, the problem must be regarded as unsolved.

Should in some measure the change be due to the acute muscular effort, the biochemical processes at the shocks would not therefore be less interesting. Such an action on the part of the organism is a psychosomatic process in which the psychic effort may be considered to be an essential factor in the mainly motor events. So, probably the changes we have established also in regard to the blood sugar are not attributable to muscular work alone. As has been pointed out from certain quarters the strong cerebral influence which no doubt is present may conceivably stimulate the sugar center in the brain—which to some extent would explain the increase in blood sugar. In regard to cholesterol, it is more difficult to resort to a similar explanation

because, as far as we know, no cholesterol-regulating center in the brain has as yet been demonstrated. On account of the abundance of lipoids in the brain, one might imagine the convulsion to be associated with a metabolic disturbance during which lipoids are given off into the blood. Still, as there exists an emotional hyperglycemia as well as an emotional hypercholesterolemia, both these phenomena are somehow correlated with the emotionality. The electric shock seems to influence the emotional state. So it seems reasonable to interpret the changes we have established as phenomena, which at least in part, are directly connected with the electric shock.

Without claiming to be able entirely to explain the effect on the organism of shock treatment in regard to the therapeutic result, however, we wish to call attention to a few interesting observations. Experiences show that the electric shock treatment is of most value in manic-depressive forms of insanity, especially melancholia. Sometimes the result is quite surprising; even after the first treatment a melancholia may change for the better without any amnesia being present as to the condition before the treatment.

In order to get a better grasp of what happens we treated some cases of psychogenic depression. We shall give a brief account of two particularly interesting cases.

The first case is that of a woman, 39 years old, who had lost her only child. The prospects of having any more children were small. She was quite broken down by the death of her four-year-old son. She could not accept what had happened, got desperate, neglected the home and showed hysterical reactions. She was always thinking about the death of her son; she reproached herself, and she also accused others. Thus, on the whole she presented a typical picture of psychogenic depression with insomnia and emotional tension. The death of her son occurred in December 1941. She was admitted to the hospital on April 20, 1942. She was then in profound despair, had fits of weeping and outbursts of desperation, on account of which she had to be removed from the department for calm patients.

Already after the first treatment she got better, and after three treatments she was restored. She was discharged from the hospital as recovered on May 11, 1942. When recovered she gave a clear account of the death of her son and of her state of health. She said that the treatment had made her calmer, so that she was able to look at her situation in a normal manner.

The other case is that of a man, 42 years old. On March 18, 1942, he lost his wife under dramatic circumstances. She committed suicide in state of melancholia, which the husband had not observed. During the first days he got along fairly well but, gradually, he began to brood over the death of his wife. He felt quite hopeless; he could not do anything without being incessantly distracted by the image of his wife. He reproached himself for not having been a better husband. His despair increased and he thought of committing suicide. However, he understood that this was "wrong" and consulted a doctor. He was admitted to the hospital on April 30, 1942. On admission he was profoundly depressed; to some extent he was aware that this was abnormal, but he could not get away from a tormenting feeling of tension and anxiety. His introspection was good, but in spite of this he could not get over his sorrow. He suffered from insomnia and was incessantly tormented by thoughts of his wife. After the first treatment he got calmer and slept better. With the second treatment his state became entirely changed. A calm attitude took the place of the tension. The desire to commit suicide was gone. He told us that though he had not forgotten what had happened and still missed his wife, the anxiety and the feeling of hopelessness had disappeared and he was able to look at his situation in a calm manner. He could even conceive the possibility of marrying again.

In regard to these cases the treatment helped the individuals in question to get over the severe depressions which arise out of a normal grief but to some extent had a psycho-pathological quality. In normal sorrows human nature has a tendency to self-healing. After some time the emotionality vanishes though the consciousness of the grief still remains. Parents who have lost

a child can talk about the event after six months or a year without feeling the emotional tension connected with acute grief. The same holds true of these patients after the treatment.

Thus the treatment seems to influence the psychophysical processes in such a manner that an idea can be "freed" from its emotional quality. In most cases a strong emotion gradually disappears. The treatment seems to promote this process and to strengthen the normal healing faculty characteristic of human nature. Therefore we have reason to assume that electric shock treatment influences psychophysical processes, manifesting themselves, for instance, in psychogenic depressions, in such a manner, that the emotional tension disappears. So we have interpreted the established biochemical changes as signs of an intervention in the vegetative nervous system. A disturbance of this system would very probably form an essential part of a strong emotion.

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THE HEREDITARY BACKGROUND OF HANDWRITING

*An investigation of the handwritings of mono- and
dizygotic twins*

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INTRODUCTION

Having passed the years of childhood, when under the influence of the teacher the handwriting is learned and adapted, a man usually continues writing in his individual manner during the rest of his life. His handwriting has become a mark of his own, just as his signature has gained legal validity. His way of writing is usually so firmly associated with himself, that the letters practically turn out to be of identical shape, whether he writes them (not draws them) with his right hand in his usual manner or, after sufficient practice, does it with his left hand either as in a normal writing or as in a catoptric one, or he writes with chalk upon the blackboard in ten times the normal size. The image of the writing, then, is more likely drawn by the brain than by the trained hand. Nor does the result seem dependent on the individual structure of the hand itself.

The variation of handwritings among people is very wide, but as expressed by the distribution of similarities and differences the variation does seem dependent on the degree

¹ The author is greatly indebted to the director of the University Institute of Human Genetics, Copenhagen, *Tage Kemp*, M.D., for his interest in this investigation, his good help and advice during its composition.

of relationship of the persons in question. It is, in fact, very often seen that different members of the same family write the same handwriting, or variations of the same. In this respect, the handwriting resembles other traits of man, the hereditary background of which we admit. The more closely persons are related, the more conspicuous are the points of resemblance between them. In this way we are led to the question of the inheritance of handwriting itself.

PREVIOUS INVESTIGATIONS

In his "Inquiries into human faculty and development" (1883) *Francis Galton* studied among others the handwriting of twins and expected to find a higher degree of conformity in their handwritings, than he actually did respecting "how strongly handwriting runs in families". Among pairs of identical twins he only found a single pair who wrote so identically that neither twin was able to recognize his own writing, but very often the handwriting would represent just the only difference between them. "It would appear", he wrote, "that the handwriting is a very delicate test of difference in organisation, a conclusion, which I commend to the notice of enthusiasts in the art of discovering character by the handwriting".

To about the same negative conclusion came *Newman, Freeman* and *Holzinger* (1937). Assuming that the handwriting is inherited and thus is in accordance with the genotype of the person, they expected to find a difference between mono- and dizygotic twins regarding the conformity of their writing. But they failed to state this difference, being probably unfortunate in their choice of methods. On the contrary the main investigation of the book renders some rather good evidence of the hereditary background of handwriting, as it seems that identical twins grown up apart exhibit handwritings which on an average are just as alike as writings of fraternal twins grown up together (see below). The likeness of the writings of some of these twins reared apart reached full identity or such a degree of resemblance, that "one might think that the two speci-

mens were written by the same person in somewhat different mood".

In order to compare Newman's material with my own, I have tried to classify the twins according to the degree of conformity of their writings, making use of the facsimiles published in the book. Five classes were used. For description of the classes see later. The result is given in the following table.

TABLE 1.

An attempt to classify 18 of the 19 pairs of identical twins reared apart and investigated by Newman et al.

Class of conformity	I	II	III	IV	V	total
Numbers of pairs	2	10	5	1	0	18

The distribution is distinctly asymmetrical and no less than 12 pairs or two-thirds exhibited rather similar handwritings in spite of the different external conditions under which the twins have grown up. This result should be compared with those given in Table 2.

Kramer and Lauterbach (1928) studied the degrees of resemblance of hanwritings of twins on one side, and of siblings on the other. They found that the correlation in the cases of same-sex twins including the identical twins are of higher value than those for opposite-sex twins and siblings. For same-sex twins they found the coefficient of correlation to be 0.82 and 0.84 for boys and girls respectively, while the coefficient for fraternal, opposite-sex twins was found to be 0.37, and the coefficients for siblings were found to vary between 0.09 and 0.27. These results indicate that the handwriting to some extent must be of genetical nature.

From the numerous German papers on the present subject one published by *Kockel* (1932) may be mentioned on account of its negative result. Kockel examined but three pairs of twins. In the following a number of papers shall be mentioned, the authors of which have that in common that they themselves believe in the hereditary nature of the handwriting, a problem they have attacked from the most different points of view.

Like the American authors, the plurality of them have tried to get a proof by comparing mono- and dizygotic twins as any

a nu blot to Himmelske
 1 der blev lyet Fred frem
 2 vender. Altes for
 b skønne Bronzer, -

a Her Højskolen L. H.
 3 Lyndesvejstetens
 b Her Højskolen L. H. H.
 Landbøjskolen Højskolen

a læst om deres Undersøgel.
 5 skal vi gerne yde vort
 b vi læst om deres Undersøgel.
 skriftet skal vi gerne g

a Jeg elsker de grønne L.
 7 med Tonerne i muggende
 b Jeg elsker de grønne L.
 med Tonerne i muggende +

for malet Edele Kva
 og Længselsskæmmet og
 og Længselsskæmmet og
 der sparker til beska

Vist skalt paa Højskolen
 blodrøde Danebrag.
 Vist skolt paa Højskolen
 blodrøde Danebrag.

de os til Undersøgel.
 titlet fra Dr. Freund
 læste en Notits om;
 n til Undersøgel.

som et befriende B.
 der nordiske Højskolen
 befriende Brødsken
 diske Højskolen med

Figs. 1—8.

Handwritings of eight pairs of monozygotic twins. In these and following facsimiles each pair is represented by a "strophe" of four lines, the partners having written two lines each. The intrageminal differences are almost undetectible. For classifications see Table 3.

Com Børn Højede b
som har Drabs Va
vare en Skrift for
tilladt mig, at sk

fik taget af os sidder i
som Sygeplejerskne b
taget af os, sidder i en b
som Sygeplejerskne her.

a have Udbytte
med Højagelse.
aa have Udbytte
med Højagelse.

I Danmark er jeg født, a
der har jeg Rod, derfra vi

I Danmark er jeg født, de
der har jeg Rod, derfra min

Der er et yndigt L a
det staaer med brei 10
mod hvorde Skuder b
hvor lyst! hvor sto

derst). Vi 4 sønner a
ger født den 15/5-18
for jeg ikke mig Tid b
at ge en fød. b

Ønsker De ellers nogle Op a
til Tjeneste. 14

Ønsker De ellers n b
vi gerne til J

Da min Foster har sk a
jeg hermed ogsaa skrive

Da De ønsker at faa 16
Haandskrift, skal vi b

Figs. 9—16.

Writings of monozygotic twins. For details see Table 3.

differences as to their specific variations would indicate the hereditary background of the investigated traits of handwriting. The general argument is that if handwriting or other traits is hereditary, one should find a high degree of conformity between related persons and a still higher degree between siblings and fraternal twins and almost identify between so-called identical twins. As compared with the, on an average, great difference between unrelated persons, the difference between the two categories of twins is but little; hence the difficulty in stating it at all.

A few authors have investigated the correlation between the handwriting and other traits of man. These studies have a more graphological aspect. Thus *Fenz* (1936) studied the connection between body-type (in the sense of *Kretschmer's*) and the general feature of the handwriting. *Fenz* grouped 257 persons into two groups, the first containing individuals described as pycnic (broad and stout), the second containing persons described as asthenic (long and thin). But by dividing them in this way he had divided them by their handwritings at the same time as well, for the handwritings in the two groups looked as if written by members of two large and quite different families.

For the following special marks of handwriting he was able to state a positive correlation to the psycho-physical type: the pycnic type was found on an average to write more regularly, steadily, slowly, broadly, "doughily", disconnectedly and heavily than the asthenic type.

Schade (1939) has worked somehow on the same line and studied the correlation between the type of handwriting and the psychic type as measured by the ability of the person to concentrate his mind upon an object. He found that the shifting, schizoid, restless mind and the irregular handwriting belonged together.

Thelen (1940) tried statistically to measure the degree of the intrageminal similarity of writings of the two categories of twins by trying to recollect in due pairs the mingled specimens of writings. He found a "contingent-quotient" of 0.73 ± 0.03 for monozygotic twins and 0.54 ± 0.057 for dizygotic ones.

Legrün (1932) was not able to demonstrate any difference between the two categories of twins of the school-age, nor that the twins on an average wrote more similarly than the average of the rest of their classmates. In his later papers (see below) this author becomes convinced of the genetic nature of the handwriting.

Frischeisen-Köhler (1930) and *Lehtovaara* (1938) have tried in quite an other way to demonstrate the difference by comparing the marks given to the pupils in writing (and other branches of knowledge given at school). They both found an evident difference between mono- and dizygotic boy-twins, but not between twin-sisters, these being probably more receptive to the instruction and the surroundings.

More graphologically detailed are the papers of *Lottig* (1931), *Hartge* (1936), *Hermann* (1940) and *Nicolai* (1940). *Lottig* found the more individual way of writing, the regularity and rhythm, to be of hereditary nature. *Hartge* studied through graphological analysis the writings of altogether 22 pairs of twins and found a somewhat greater conformity within mono- than within dizygotic pairs. She cautions against a too quick judgment of the dissimilarities between twinwritings. In a special case the "first impression" classified two writings as being evidently different, but on studying them systematically she found no less than 28 points of similarity against only 5 of dissimilarity. *Hermann* and *Nicolai*, both being pupils of *Bracken* (see below), investigated statically the writing angle and the breadth of the bases of letters and found these traits to be hereditary.

Carmena (1935) investigated the hereditary nature of handwriting by studying the specific pressure of the pencil upon the paper using a so-called "Kraepelin's balance", an instrument which automatically reproduces the pressure in a diagram. By this method he was able to demonstrate an indisputable difference between mono- and dizygotic twins. The twins investigated were divided into three groups according to the differences between their diagrams. Pairs showing very small differences were reckoned as the first group. More than half the number

of monozygotic twins or 16 out of 29 pairs were reckoned in this group, as against only 2 out of 21 dizygotic pairs.

Bracken (1939) examined the speed of writing and found it to be more conform within monozygotic pairs than within dizygotic ones. Like *Carmena* he also investigated the writing-pressure and found it hereditary if one took the special sources of errors into consideration, namely the "exchange of parts", which very often takes place between monozygotic twins, one of whom being, then, the "ambassador" of the pair. The pressure-curve proved to be more characteristically different between grown-up twins.

In a paper from 1937 *Legrün* in four examples illustrates the possibility of increasing likeness of the handwritings of twins grown up apart. Being through some of the previously mentioned papers convinced of the hereditary nature of handwriting, he (1938) investigates the possible causes of actual differences met with. In this paper he also shows that the personal identify between a person and his "alter ego" may show up in their handwritings too.

PRESENT INVESTIGATIONS

The aim of the present study is to investigate the correlation between the handwriting and its genotypic background. This problem I have tried to solve by seeking answers to the following two questions: *firstly, whether there is any positive correlation between the handwritings of relatives as might be seen through a comparison of handwritings of twins on one side and handwritings of pairs of unrelated persons on the other; secondly, whether a difference is present between the categories of mono- and dizygotic twins.* A positive answer to the first question would tell us that handwriting as such is inherited to a smaller or greater degree; the answer to the second question would determine whether such an inheritance is biological or false by way of personal influence. For any difference found between the two categories of twins will, argue against the very common

assumption that the handwriting is an "acquired" character which reaches its expression mostly under the influence of the surroundings at school or at home or merely develops at random.

The material of the investigation has been obtained through a newspaper inquiry and by an appeal in a periodical publication for the board schools in the country. In this way I was very kindly furnished with specimens of handwritings of sixty pairs of adult twins and about a hundred pairs of children. In addition, the letters from the senders gave me the wanted information as to the sex, names, age and natal origin of the twins and sometimes a description of their likeness. For reasons mentioned below, the handwritings of adults and children were kept apart and examined separately.

To the category of adults were reckoned persons beyond the school age, *i.e.* 15—17 years of age. At this age the handwriting has begun attaining its personal style which, as a rule, is almost independent¹ of the instruction received in the school-days, which will be discussed later. Irrespective of the differences in age and school instruction, the handwritings of adults may therefore be compared directly and judged by a scale common to them all. In contrast hereto, the age and the different steps of development as well as the varieties of instruction given to the children play an overshadowing part in the appearance of their handwritings, and thus make a direct and true criticism impossible unless the children are of the same age and from the same school-class. The methods, therefore, had to be in some respects different in the cases of adults and children. *Common to both methods is the comparison of the handwritings in pairs.*

a) *The investigation of handwritings of adult twins.*

The specimens received were provided with progressive numbers and the writer's name, sex and origin were recorded, where-

¹ Illustrated examples have recently been published by R. H. Pedersen (1943).

a Gert af Randeborn
 17 Kiel, sluttede Vær
 skal med danske
 b Christoffer ud af

a Jeg kuypt nokken
 19 penne vore af pengene
 b J. haft i alder 1
 legi feldt i milden

a De sikker ved telefon
 21 delse til min Broder
 b De sikker ved tele
 delse til min Broder
 . paa Lindholm.
 Mund = og Klove og

a fortalt Dem lidt
 18 vi er og hvilken
 ansat i Statens
 b Forhaabentlig vil

a at der ikke findes nog
 20 vore Skrifter. Selv kan
 b Saaferm denne Prøve
 Hjelp i Forskningerne,

a idet jeg haaber a
 22 min Assistance
 b Og udbød hende
 jeg modtaget

formodt Ræen betydelig
 Klovsyge = Stationen paa

23

b

Figs. 17-23.

Writings of monozygotic twins. Specimens represented by Fig. 19 have been written by two brothers reared apart. See also Table 3.

a onig meget. Jeg
 24 i Prove af min Skrift,
 b Prove af min Haand
 idet jeg går op

a Og saa kimede Te
 26 Lighedem. Han k
 b Og saa kimede Telefor
 igheden Han kunde

a se hvor eta
 28 der er jo a v
 b jeg ikke - men
 hvidende til en

kan nas den ikke sande
 og blamé skær ved den
 by ind til Hovindskeden
 Helligere Besig erindrede

og enhver Drenge vil misunde
 fred hans spændende Tilværelse
 unde Henry de Monfreid
 spændende Tilværelse.

Undersøgelser, om Minuskeine
 sager Haandskrift i Arv og
 søghele, foruden Zungen
 Haandskrift i Arv og den

Figs. 24—29.

Writings of monozygotic twins. Showing unusually great differences.

For details of classification see Table 3.

after the sheets were folded in such a way that anything giving information as to their origin was covered. Then the handwritings were compared in pairs. The comparison done, the pairs were divided into groups of mono- and dizygotic twins according to the information recorded and then counted.

By the work of comparison a scale with 10 degrees of difference was used while the results for the sake of clearness have been presented in five double-classes. These classes of conformity

comprise the following categories of pairs, whether of twins or of unrelated persons (see below):

Class I: pairs whose partners write identically or very similarly (cf. Figs. 1 to 13).

Class II: pairs exhibiting handwritings, which without being fully identical still bear the same stamp or "familial" mark, being but variations of the same theme (cf. Figs. 14—23).

Class III: pairs with handwritings of mutual middle-difference, viz., they differ in such a way that the similarities, so to speak, balance the differences. This class should be the largest if the persons compared are totally independent of each other, as when paired at random. Specimens given in Figs. 24—28 have been reckoned in this class.

Class IV: pairs writing fairly differently. (An example is given in Fig. 29.)

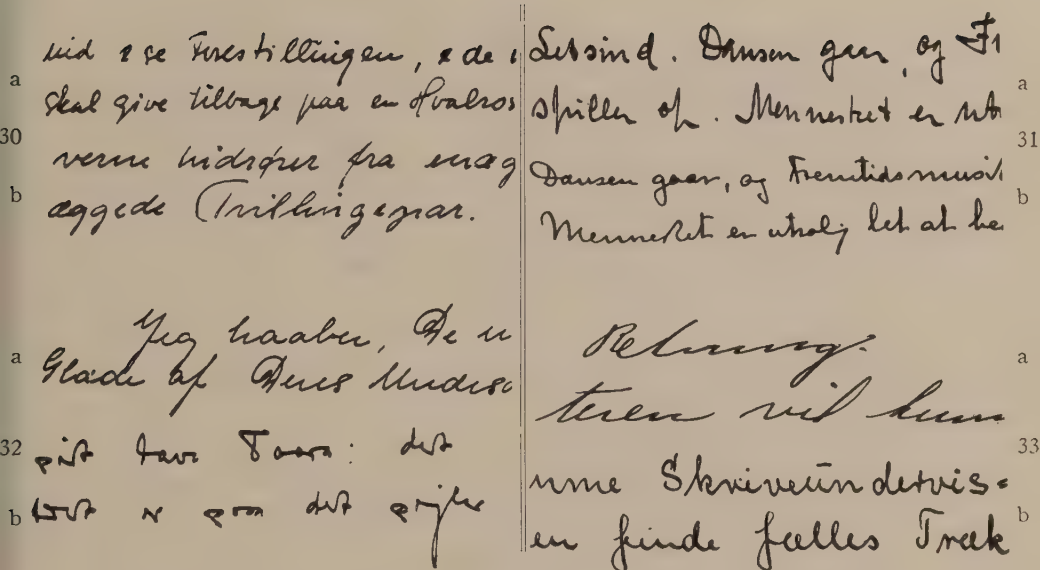
Class V: pairs writing very differently or as differently as imaginable. (Figs. 32 and 33 have been classified as belonging to the lower half of this class.)

The judgment was based on an estimate and took as far as possible into consideration the different features of the writing, its pressure, its general point of development or degree of emancipation from the model, its form, its degree of regularity and so on. In order to make a counter-test of the scale used and to get a picture of the variation of differences between un-

TABLE 2.

Distribution of pairs of handwritings as classified according to their degree of conformity. For description of classes see the text. A: distribution of random pairs; B and C: that of mono- and dizygotic twins respectively.

Classes of conformity (double-classes)	I	II	III	IV	V	Total
	Numbers of pairs					
A: random pairs	1	16	28	17	1	63
B: monozygotic twins (see Figs. 1—29)	13	10	5	1	0	29
C: dizygotic twins	4	12	9	4	2	31
B + C	17	22	14	5	2	60



Figs. 30—33.

Handwritings of dizygotic twins showing small and great differences.

Fig. 32 written by same-sex twins, sisters, the remaining ones by opposite-sex twins.

related persons, the specimens of handwritings from the twins together with those from 6 other persons were paired at random and judged. Table 2, A, gives the result of one "cast". The reader may convince himself of the difference between *intrageminal* differences on one side and *intergeminal* differences on the other through a comparison of, for instance the facsimiles of Figs. 1-8.

The distribution curve for random pairs of handwriting specimens turned out to be, as expected, a symmetrical curve with its modus in class III. As compared to it, the curve B + C is asymmetric with its modus in class II, indicating that the degree of relationship and degree of resemblance in handwriting are correlated. *Related persons most often write "related" handwritings.* The asymmetry is still more pronounced in curve B, which is totally one-sided, indicating that a *high degree of similarity reaching identity is the normal feature of the hand-*

TABLE 3.

List of facsimiles.

The figures comprise the facsimiles of the handwritings of 29 pairs of monozygotic adult twins, being the entire material of this category studied. In addition they give facsimiles of 4 pairs of dizygotic twins showing different degrees of variation. The persons are represented by two lines each. Thus a "strophe of four lines" represents a pair of twins. The different columns give the figure number, the class of concordance (1 to 10), the sex and the age of the persons. The right column contains some remarks of general interest.

Fig. No.	Degree of difference 1—10	Sex	Age years	Special remarks
1) <i>Monozygotic twins.</i>				
1	1	♀	22	Different instruction during the first two school years.
2		♂	—	—
3		♀	24	Now a clerk and a hospital nurse, respectively.
4		♀	49	—
5		♂	15	Are both going into apprenticeship.
6		♀	64	Write: "We are very much alike and are often mistaken by people when we are not together. We have got the same small shortcomings, and we very often think the same at the same time."
7		♀	17	—
8		♀	24	—
9		♀	44	Write: "Our views of life are and have always been identical, and when one of us is ill the other most often is ill too."
10	2	♂	18	—
11		♀	23	In childhood they were examined by the late Prof. O. Thomsen, who convinced himself of their identity.
12	3	♂	58	—
13		♀	29	—
14		♀	30	"International dancing duo".
15		♀	61	—
16		♀	26	—

TABLE 3 (cont.)

Fig. No.	Degree of difference 1—10	Sex	Age (years)	Special remarks
17	3	♀	22	The sender, their teacher, who, has known the girls for 10 years, is still not able to distinguish them.
18		♀	24	
19		♂	27	Identical twins born in Iceland. Parted when $\frac{1}{2}$ year of age and brought up apart in neighbouring villages. Met and played together sometimes. When 14, they went to the same school for one year. Students (linguistic and mathematic). Now a meteorologist and an engineer, respectively.
20		♀	29	
21		♂	38	
22	4	♀	41	Write: "We are like two drops of water". One of the brothers, <i>a</i> , is blind. Both artisans, have both had a duodenal ulcer.
23		♂	70	
24	5	♂	37	
25		♀	28	
26		♀	—	
27	6	♀	15	
28		♂	50	
29	7	♂	25	Clerk and grocer.

2) Dizygotic twins.

30	2	a♂, b♀	20	—
31		a♂, b♀	55	—
32		a♀, b♀	37	Write: "Regarding our appearance and character we are as different as our handwritings indicate".
33	9	a♂, b♀	20	

writing of identical twins. The dizygotic twins show, on the other hand, a greater variation as to the differences between their writings. This is in accordance with their greater genotypical idiovariation. This difference stated between the two categories of twins answers positively the second of the two questions put forward, and indicates that handwriting is a character *which is dependent on biologically inherited abilities.* This will also be discussed later.

Figs. 1—29 give facsimiles of all the specimens received from monozygotic twins. More detailed information is given in Table 3.

b) *The judgment of school-children's handwritings.*

On application to about twenty teachers, the writer was kindly furnished with specimens of handwritings from the classmates of 27 pairs of twins whose handwritings were already received. 10 of these pairs were reported as being monozygotic and the remaining 17 as dizygotic twins 9 of the latter group being pairs of opposite-sex twins.

It was my aim to use the classmates of the twins as a background for a comparative judgment of the differences between their handwritings, as I wanted a method which enabled me to leave out of consideration the differences caused merely by differences in age and instruction given.

The classes appeared to be very different as to the degree of methodic training given them. Some classes wrote fairly homogeneously, so to speak, while others showed a greater variation of types of handwritings. But in most cases each class had its own appearance, the result of the instruction (cf., for instance, Figs. 34 and 35). The former illustrates a "well-drilled" class, while the pupils of the latter show a greater individual variation, although they still have some features in common. Even in the first case the individuality of the boys peeps out. In both classes the identical twins (marked A and B) appear to have the same handwriting, what is easily seen. But in other school-classes the twin-siblings appeared to write more differently, but due to the aforementioned class-individuality it

A Da jeg første Gang fik Inter
 B Da jeg første Gang fik I.
 Da jeg første Gang fik Inter
 Da jeg første Gang fik Interesse
 Da jeg første Gang fik I.
 Da jeg første Gang fik Interesse
 Da jeg første Gang fik
 Da jeg første Gang fik I

Fig. 34.

Handwritings of pair No. 1 of monozygotic twins, A and B (boys), and six of their class-mates. Each person represented by one line. Note the general effect of the teacher's instruction.

A blide, og hun maatte staa

B blide, og hun maatte staa

Der var engang en Dronning, som

Det var engang en Dronn

Der var engang en Dronning, so

Det var engang en Dronning s

Der var engang en Dronning, se

Der var engang en Dronning

Det var engang en Dronning so

Der var engang en Dronning, so

Der var engang en Dronnin

Fig. 35.

Handwritings of pair No. 9 of monozygotic twins, A and B (girls) together with their class-mates. Note the variation and in spite of that the common outlook of the handwritings due to the instruction given.

TABLE 4.

Distribution of classmates used as a background for a judgment of the relative distance between the handwritings of twins of school-age.

Numbers of classmates at the different distances (classes of concordance) from one and the same twin designated as A. The A's are placed on the 0-line, while the positions of the B's are marked with a letter.

Classes of conformity				I	II	III	IV	V	VI	VII	VIII	IX	X	
Class-limits				0	1	2	3	4	5	6	7	8	9	10
Class-value				0.5	1.5	2.5	3.5	4.5	5.5	6.5	7.5	8.5	9.5	
No.	Sex	Age	Means of classes											Total No. of classmates
Monozygotic twins														
1	♂	Fig. 34 13	2.0	1	9	9	1							20
				A-B										
2	♂	11	3.1		2	5	5	1	1					14
				A-B										
3	♂	10	3.4		3	5	4	7	1					20
				A - - B										
4	♂	14	3.8		1	1	3	4	1					10
				A - - B										
5	♀	9	3.8		6	6	6	1	3	7				29
				A-B										
6	♂	15	3.9		2	3	6	6	1	3				21
				A - - - - B										
7	♀	16	4.1			6	6	9	3	2				26
				A - - - - - B										
8	♀	10	4.3			4	8	6	7	2				27
				A - - B										
9	♀	Fig. 35 10	4.7			1	2	3	1	1	1			9
				A-B										
10	♂	13	4.8			1	7	8	7	3	1			27
				A - - - - - B										
Average				A-B = 1.7 (Classes)										203
Dizygotic twins														
11	♀♀	11	1.7	4	10	5	2							21
				A-B										
12	♀♂	8	3.2		6	7	3	5	2	1				24
				A-B										
13	♂♂	14	3.3		6	5	5	4	4					24
				A - - B										
14	♀♂	13	3.4		1	3	2	1		1				8
				A - - - - - B										

TABLE 4 (cont.)

Classes of conformity				I	II	III	IV	V	VI	VII	VIII	IX	X	
Class-limits				0	1	2	3	4	5	6	7	8	9	10
Class-value				0.5	1.5	2.5	3.5	4.5	5.5	6.5	7.5	8.5	9.5	
No	Sex	Age	Means of classes	I	II	III	IV	V	VI	VII	VIII	IX	X	Total No. of classmates
15	♀♂	12	3.5		1	1	1	1	1					5
				A	-----	B								
16	♀♂	14	3.8			2	2	2	1					7
				A	-----						B			
17	♀♀	11	4.3			1	1	1	2					5
				A-B										
18	♂♂	11	4.5			1	10	6	3	3	1			24
				A	-----					B				
19	♀♂	8	4.6		1	4	6	7	7	5	1			31
				A	-----					B				
20	♀♂	9	4.7			1	7	8	6	4				26
				A	- B									
21	♀♂	9	4.8					2	1					3
				A	-----	B								
22	♀♂	8	4.8		1	5	4	3	6	5	2	1		27
				A	-----	B								
23	♀♀	11	4.9			3	5	9	9	4	1	1		32
				A	-----	B								
24	♂♂	11	5.0		1	2	3	11	4	6	3			30
				A	- B									
25	♀♀	12	5.4			1	4	3	4	7	1	1		21
				A	-----					B				
26	♀♀	11	5.5			1	8	6	5	7	6	1		34
				A	-----	B								
27	♀♀	13	6.3						1	2				4
				A	-----	B								
Average				A-B = 2.7 (Classes)										326

seemed impossible to get a true and direct judgment of the personal variation of the pairs of twins, for which reason the following method was chosen.

Due to the varying degrees of variation within the different classes I was forced to use different scales in the different classes, broad scales in some classes, narrow ones in others

having well-trained pupils. But using one of the twins in each class as basis for the measuring, I was able to get a measure of the *relative distance* between the twin-siblings with the variation of their classmates as a background.

The twin-partner used as basis in each class was designated A, while his brother or sister was called B. The relative distance between A and B was then obtained simply by counting the classmates who, in regard to the type of handwriting, were nearer to A than B or were placed outside B. If A and B vary independently one would, on an average, expect to find the same number of classmates on either side of B, but this appeared not to be the case, as will be seen from Table 4, in which the classes have been divided into two groups, classes with monozygotic twins and classes with dizygotic ones. Within the groups the classes have been arranged according to the numerical distance between A and the class-mean. The grouping of the classes took place after judgment.

From the table it is seen that with but few exceptions all the B-twins are placed somewhere between their A-mates and the mean of their classes. Although the relative distances between the twins vary to a great extent, they are "coupled"

TABLE 5.

Actual and expected distributions of classmates of twins in regard to their handwritings.

	Numbers of class-mates			Total
	to the left of B	on the same line as B	to the right of B	
In school-classes with mono- zygotic twins	20	36	147	203
or 12 %	—	—	88 %	(167)
In classes with dizygotic twins	50	37	239	326
or 17.3 %	—	—	82.7 %	(289)
Expected when A is inde- pendent of B	228	(73)	228	529
or 50 %	—	—	50 %	(456)

somehow, as they lie nearer one another than a random placing of the B-mates would predict.

529 children in all were used as backgrounds. Out of these, 73 children fell on the same line as the B-mates. The distribution appeared to be asymmetrical, as only 12 and 17.3 per cent of the classmates fell to the left side between A and B instead of, as expected, 50 per cent. The details are given in Table 5.

It is seen that the asymmetry is still more pronounced when classes with the dizygotic twins have been left out of consideration. 17.3 minus 12 per cent indicate the possible difference between these two categories.

The remaining part of children's handwritings in my collection were judged as far possible. A great part of the twins resembled each other as expected. A few of them wrote identically. But due to the great divergences as to age and instruction no statistic treatment of the data was practicable.

DISCUSSION

Both series of investigations showed that the degree of resemblance between handwritings increases with increasing relation between the individuals. Thus the greatest degree of conformity was found between identical twins, several pairs of whom exhibiting fully identical handwritings. *In both series the pairs of dizygotic twins showed the wider variation of handwriting, yet still a far smaller variation than that showed by pairs of unrelated persons.*

The points of resemblance observed between monozygotic twins were remarkable. Out of 29 pairs, no less than 13 had handwritings which deviated from partner to partner but to so slight a degree, that they looked as if written by the same person, maybe sometimes in a different mood. Of the remaining pairs 10 could be described as writing fairly similarly. Only 6 pairs showed a mean difference as that found between handwritings of non-relatives. But even in these few cases, the handwritings did not differ to such a degree that all traces of similarity had

been lost. In fact, in regard to certain fundamental factors as to the pressure and state of development, the twins were very similar still (see, for instance, Figs. 24, 25 and 29). None of the monozygotic twins were found to write as differently as did some of the dizygotic pairs. This justifies the postulate *that identical twins most often write identically or at least very similarly*. Further, we may therefore conclude *that the general appearance of a man's handwriting in its fundamental characteristics corresponds to his hereditary type, while the possible deviations as seen between identical twins expresses the varying penetration of the type and the limits of its phenotypical expressions*.

The handwriting is, no doubt, a primarily "acquired" character on which account any resemblance observed between writings of kinsmen very often has been explained as being due to some "family tradition" or to a common instruction at school. On the other hand, as also suggested by *Newman*, neither of these external factors should be able to distinguish monozygotic twins from fraternal twins, furnishing the latter category with greater possibilities of deviating than the former. Both categories are expected to vary to about the same extent as, on an average, they have been exposed to the same external influences. But they were found to be different and this difference must be correlated to internal differences between the two categories. The handwriting i.e., the individual way of writing, has a genetic background. The handwriting is, so to speak, the phenotypical expression of a certain genetical disposition of carrying out, in an individual manner, that special piece of work. The same "manner" may individualize other acquired abilities, and the handwriting, therefore, is probably only one of the outward appearances of the individuality. Handwriting has a genetical background, but is not of course inherited like an instinct.

The fact that the category of dizygotic twins includes pairs of opposite-sex twins, may perhaps seem to be able to explain the said difference. But it was found that opposite-sex twins and pairs of same-sex fraternal twins were equally represented in the different classes of concordance. In fact, the difference

in writings between twins is independent of the sex; and furthermore it has never been possible for graphologists with certainty to determine the sex of the person by the handwriting.

The resulting handwriting of a person seems rather independent of external factors and the writings of two brothers or a brother and his sister may turn out to be alike in spite of different surroundings and instruction, or unlike in spite of identical external influence. Fig. 19 gives the facsimiles of the writings of two identical twins, brothers, who have been brought up apart from one another; until their 15th year they have had different instruction. They now have handwritings that are like variations of the same theme. Fig. 33 gives the handwritings of a young man and his twin-sister. They have especially informed me of their identical instruction in writing during the school-days, they write extremely differently and neither of them like the model learned.

Great resemblance is often seen between the handwritings of *parents and offspring*, in spite of the differences in instruction the two generations have had. Fig. 36 shows the handwriting of a father and his son. Both writings were written when the persons were about 20 years of age. The father died when the son was still a little child, and in spite of differences in instruction and the absence of any possibilities of personal influence, their handwritings have followed the same course of development. Fig. 37 gives another example of similarity of handwriting between a father and his son. The specimens are written on the very same day; the resemblance is obvious here, too.

Therefore, as the handwriting seems to develop rather independently of the external conditions, the greater part of the similarities and differences observed between twins must be due to an overshadowing influence of the genotype. Although the handwriting so evidently is an acquired dexterity as learned by training and developed under the control of the teacher, it nevertheless always or nearly always deviates from the model, following its own course as if inevitably.

If handwriting, then, with its possibilities of phenotypical

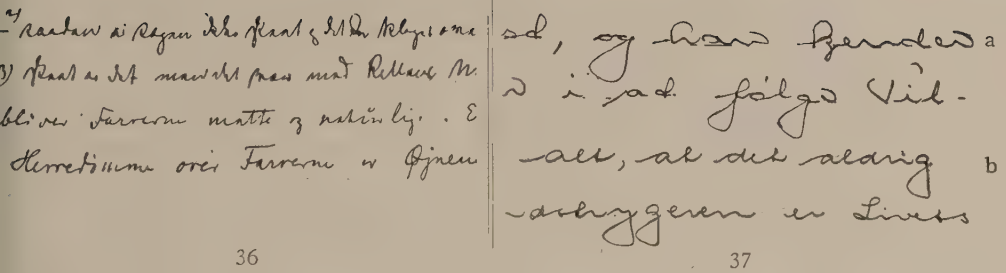


Fig. 36.

Specimens of handwritings written by a father and his son when both were of about the same age. a, the fathers handwriting about 1869; b, that of his son about 1899. The letters of the former are gothic, while those of the latter are latin. See also the text.

Fig. 37.

Writings of a father and his son written on the same day.
See also the text.

variation for its greater part is an inheritable trait of man, it is without doubt dependent on a multitude of factors, making the usual genetic analysis difficult like the analysis of other complex characters of man.

The present paper is in agreement with the majority of the previous papers on the subject. It differs from them in taking into consideration also the variation of handwriting of unrelated persons and the classmates and by letting the variation of classes and random pairs serve as backgrounds for the comparison between mono- and dizygotic twins.

SUMMARY

1. Specimens of handwritings from 60 pairs of adult twins were judged according to the method of concordance. Divided into five classes a one-sided distribution was found in the case of 29 monozygotic pairs of twins (cf. Figs. 1-29), while 31 pairs of dizygotic twins had a curve of distribution which lay between the above mentioned one-sided curve and the distribution of the

same specimens but this time paired at random. The latter curve appeared to be like the ideal binomial curve (see Table 2).

13 out of the 29 pairs of monozygotic twins proved to write almost identically, while only 4 out of the 31 pairs of dizygotic twins did so. Of the random pairs, only 1 out of a total of 63 could be reckoned in this class.

2. Using their respective classmates as background the relative distances were measured between the partners of 27 pairs of twins in the school-age. It was stated that on an average the distance between twins is smaller than the distance between one of the twins (used as basis) and the average of the class. The twins were found to be "coupled" in regard to the appearance of their handwritings. In both series this "coupling" appeared to be greater between monozygotic twins than between dizygotic ones, indicating the true hereditary background of the handwriting.

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